



# A.M.A. ARCHIVES OF NEUROLOGY & PSYCHIATRY

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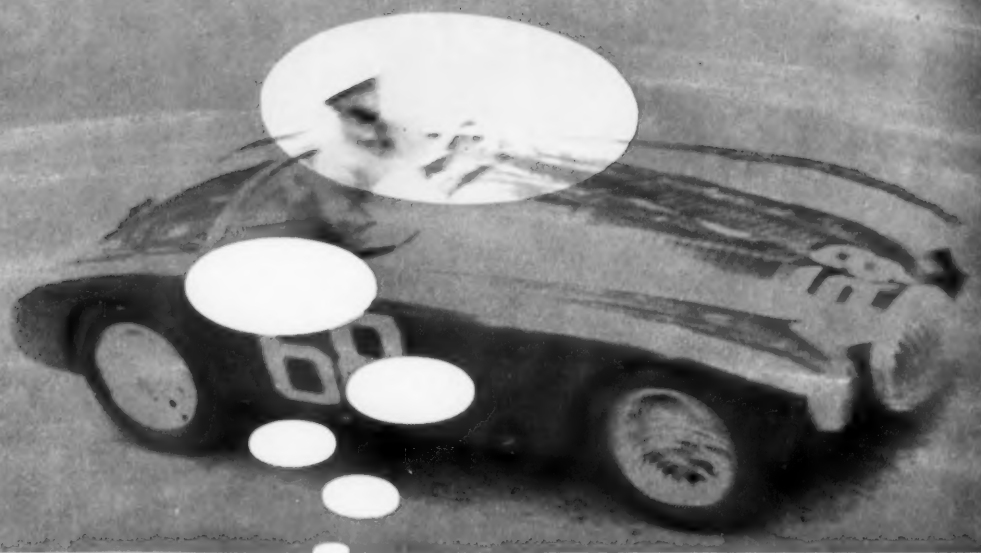
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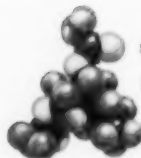
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## SECTION ON NEUROLOGY

### Meralgia Paresthetica

HAROLD STEVENS, Ph.D., M.D., Washington, D. C.

The symptoms of meralgia paresthetica are pain, numbness, itching, or other dysesthesias occurring in the distribution of the lateral femoral cutaneous nerve of the thigh, that is, over the anterolateral aspect of the thigh, usually in an elliptical patch and usually unilateral. In this area perception of pinprick and touch often is diminished or lost. There is no motor disturbance; the lateral femoral cutaneous nerve is entirely sensory.

Many writers are patently incorrect in describing this condition as rare. Other inconsistencies and contradictions in the literature are regularly found, particularly in regard to age of onset, predilection for one sex, course, prognosis, and treatment. The literature on the etiology of meralgia paresthetica is particularly obfuscating. The multiplicity of ascribed causes, often asserted with strong conviction, further signalizes the need for accumulation and clarification of data on this common affliction.

This syndrome often is diagnosed incorrectly and misconstrued by the patient or practitioner as representing a sinister disease process. It is noteworthy that patients with this disorder may consult or be treated by physicians in a wide range of

specialties. In addition to the general practitioner, the patient with meralgia paresthetica may be seen first by the internist, orthopedist, obstetrician, or surgeon. This testifies to the wide variety of diseases or conditions under which meralgia paresthetica may appear. Friedlander,<sup>1</sup> whose patients were exclusively military personnel, found meralgia paresthetica to be the commonest mononeuritis, but none of his 14 cases had been correctly diagnosed.

The group of 42 cases reported here were all examined by me in the framework of private neurological practice, either in the private office or at the Group Health Clinic, a prepaid private medical plan in Washington, D. C. All patients were professional or other types of white-collar workers, or housewives.

Many articles on this (and other neurological entities) fail to define the sampling situation, and this may account for some of the disparities and contradictions in the literature of this syndrome. Many of these patients were seen or referred for reasons other than the presence of meralgia paresthetica. Most cases were found simply by making specific inquiry regarding subjective sensory disturbances over the thigh, or by making a careful sensory examination in the zone of distribution of the lateral femoral cutaneous nerve. Thus, the relatively large number of cases unearthed with this approach testifies to (1) the frequency and (2) the benignity of this disorder. Other reported observations deal exclusively

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Professor of Neurology, George Washington University School of Medicine.

Read before the Section on Nervous and Mental Diseases at the 105th Annual Meeting of the American Medical Association, Chicago, June 13, 1956.

with patients whose symptoms are severe enough to motivate them to seek medical attention. This would tend to weight the literature in favor of the severer cases.

A few of the patients seen for reasons other than meralgia paresthetica were unaware of the patch of hypesthesia, or only after it was outlined could they recall having had subjective sensory experiences. Only 16 of the 42 patients came for medical examination because of paresthesia (Table).

*Reason for Referral for Neurological Consultation*

	No. of Cases
Meralgia paresthetica	16
Bell's palsy	1
"Check-up"	1
Headache	2
Parkinsonism	3
Multiple sclerosis	2
Tremor (hysterical)	1
Myasthenia gravis	1
Protruded lumbar disc	9
Cervical disc	1
Acroparesthesia	1
Bursitis (shoulder)	1
Dysphagia (hysterical)	1
Convulsive disorder	2

Another factor that influences the statistics of meralgia paresthetica is that few, if any, patients are admitted to a hospital with meralgia paresthetica. Thus, the conventional practice of sampling clinical data from accumulated hospital records of this condition would yield few, and only biased, data. Only one case was classified under this diagnosis at George Washington University Hospital in a total of 100,000 admissions in the last seven years.

Thus, this problem is almost exclusively one in minor neurology and perhaps for this reason has provoked meager interest, particularly among contemporary American and British neurologists. The older German literature is replete with clinical reports following Bernhardt's<sup>2</sup> two-and-one-half-page article and Roth's<sup>3</sup> brief monograph, publications which appeared independently in 1895. Roth had previously read a paper on this subject before the Physico-Medical Society in Moscow. He reported 14 cases and is responsible for the label "meralgia paresthetica," which means pain and paresthesia in the thigh. It is also known as

the Bernhardt-Roth syndrome. Actually, Hager<sup>4</sup> had given a precise but briefer description, including surgical treatment, 10 years before. Since Roth's monograph many individual cases have been reported,<sup>5-10</sup> and sporadic reviews have appeared. Lievre and Bloch-Michel,<sup>11</sup> in 1953, in a 10-page article, claimed that a precise description of this syndrome has not been published since the original accounts of Roth and Bernhardt. However, several comprehensive treatments of the subject can be found, including a particularly thorough disquisition by Mendel<sup>12</sup> in 1933 and descriptions by Klimke<sup>13</sup> (1929) and by Mennen<sup>14</sup> (1933). A prior review was published by Sabrazès and Cabannes<sup>15</sup> in 1897, and another complete article, in Paris by Brisard<sup>16</sup> in 1900. The last is a 99-page monograph, summarizing the background, theories of causation, clinical aspects, etc., with 42 references. Another review was published by Musser and Sailer<sup>17</sup> in 1900, in which they collected 89 cases from the literature and added 10 of their own. Ecker and Woltman<sup>18</sup> reviewed the records of the Mayo Clinic in 1938 and summarized these data. A briefer review was published by Schachter<sup>20</sup> in 1945. Many individual case reports faithfully reiterate the essence of these prior, more complete articles. Some contribute new, but often contradictory, data with respect to the incidence, treatment, and etiology.

Disagreement on the incidence of this syndrome has persisted throughout the 60 years that it has been known. Ecker and Woltman<sup>19</sup> said that their 150 cases represented 3 out of 10,000 patients examined at the Clinic. During the same period 5316 cases of other forms of neuritis occurred. These authors considered the syndrome uncommon. It was believed "not very common" by Musser and Sailer,<sup>17</sup> who stated that the symptoms are frequently so severe as to disable the patient and oblige him to seek medical advice. "Many on the watch for meralgia paresthetica never see a case." It was considered "rare" by Chavany,<sup>21</sup>

Viets,<sup>22</sup> and Reichert.<sup>23</sup> In recent editions of texts on neurology, it is called "uncommon" by Walshe<sup>24</sup> and also by Purves-Stewart.<sup>25</sup>

Contrary opinion was expressed by Brisard,<sup>26</sup> who considered the syndrome relatively frequent. Mendel,<sup>12</sup> noting 32 cases personally, and Krabbe and Ellerman,<sup>26,27</sup> 15 cases, stated that it was not a rare disease. Lievre and Bloch-Michel,<sup>11</sup> reporting 42 cases, and Schneck,<sup>28</sup> reporting 21 cases, believed it to be common. King<sup>29</sup> called it relatively common; Miller,<sup>30</sup> fairly common, and Friedlander<sup>1</sup> believed it was not uncommon but overlooked and misdiagnosed. Corlette,<sup>31</sup> in 1944, stated:

The disease is not often referred to and it is probable that medical practitioners in general know very little about it. That is not because it is uncommon, as some have thought, but it is in most cases not conspicuously assertive.

It is apparent from the 42 cases I have personally encountered in a period of seven years that meralgia paresthetica is common.

Disagreement persists regarding the distribution of the syndrome between the sexes. Most writers emphasize that the greater number of sufferers are male. Bernhardt,<sup>2</sup> in his initial report, had all middle-aged male patients. In Roth's<sup>3</sup> series there were 12 men and 2 women. Schlesinger,<sup>32</sup> in 1900, had nearly four times as many men, and a similar proportion was observed by Mendel.<sup>12</sup> A ratio of male to female of 3:1 was found in the 150 cases from the Mayo Clinic, corresponding to the ratio found in Musser and Sailer's<sup>17</sup> series. Atkinson<sup>33</sup> found 259 cases in the literature in 1938, of which 84 were of women. Schachter found twice as many male as female patients in his series. Brain<sup>34</sup> believed that the disease usually affects middle-aged men, and Goldstein<sup>35</sup> stated it was commoner in men.

However, Fischer and Krieg<sup>36</sup> found it predominantly in females. In the 42 cases reported here, the male-to-female ratio was 1.6:1.

Mendel<sup>12</sup> and Musser<sup>17</sup> attribute the preponderance of men with this affliction to typical feminine reticence. Some writers

attribute it to occupational factors.<sup>37</sup> Wilson<sup>38</sup> states that men are on their feet more—for example, in occupations as soldiers, sailors, waiters, etc. In contrast, Roth<sup>3</sup> blamed the sedentary way of life; he found the condition more frequent in fat men with hemorrhoids and varicosities. Mack,<sup>39</sup> in 1946, also found it commonest in men with an obese, protuberant abdomen. A long list of predominant male occupations has been found in association with meralgia paresthetica and blamed for its cause, including those already mentioned and, in addition, those of blacksmiths, smelterers, domestic workers, tailors, shoemakers, mechanics, stokers, cabinet makers, delivery men, etc. Roth, however, stated that no laborer has ever been known to have it. Physicians, for reasons not known or not clearly stated, are frequently victims. One of Bernhardt's<sup>2</sup> patients was a 51-year-old physician. Of the 99 cases of Musser and Sailer,<sup>17</sup> 10 were physicians. Curschmann<sup>40</sup> reported six cases. One of Rennie's<sup>41</sup> three cases was a physician, who had a bilateral patch of hypesthesia and feared that he had locomotor ataxia or some other serious cord disease. One of three physicians reported by Neuhaus<sup>42</sup> also feared tabs. Goldstein<sup>35</sup> mentioned two cases in physicians and Bonica<sup>43</sup> one case of a physician out of three. Several physicians have reported their own cases, in vivid and polysyllabic language.<sup>44-47</sup> Sigmund Freud's own case report was published in 1895 as an instance of "Bernhardt's syndrome."<sup>47</sup> Corlette<sup>31</sup> reports his own case and adds that he knows of five among his colleagues.

This apparent frequency of meralgia paresthetica among physicians should not be attributed hastily either to a sedentary way of life or to professional panniculitis. It merely testifies to the essentially benign nature of this syndrome, notice being taken oftener by physicians only because the symptomatology exceeds their relatively lowered thresholds. Two physicians are included in this group; four others are known that have the disorder, but I have not examined them.

The age of onset is usually after 20. Hager<sup>4</sup> reported this condition in a 21-year-old girl. Goldstein<sup>35</sup> describes it in an 11-year-old boy and in his 8-year-old brother. Dopfer<sup>48</sup> records a 10-year-old patient, and Rennie,<sup>41</sup> a 19-year-old girl whose symptoms had begun two or three years before. Escat's<sup>44</sup> own case appeared at the age of 18. Roth found the ages of patients to be between 36 and 55. Tobias<sup>49</sup> found the preponderance of cases between the fifth and the seventh decade of life, and Mennen,<sup>14</sup> between the third and the sixth decade. In 76% of the Mayo Clinic patients symptoms first appeared between the ages of 20 and 59. Schachter<sup>20</sup> recorded the age when the diagnosis was made in 128 cases in the literature, as follows:

Age, Yr.	No. of Cases
Under 20	5
20-40	52
41-60	64
60+	7

Schneck<sup>28</sup> questioned the generalization that meralgia paresthetica is a disease of middle age; his 21 patients from military life had an average age of onset of 27.7 years.

In the 42 cases reported here, the age of onset is between the ages of 10 and 69, with a mean of 39.8 for the whole group. This age is younger than for most series, and, again, it may reflect a different population (Fig. 1).

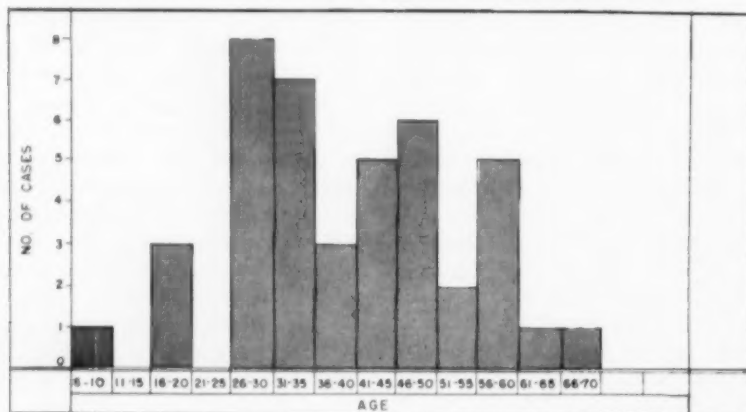
The average age was 34.0 years for the 16 females and 43.3 for the males, with a standard error of the mean of 3.17 and 2.62, respectively. The standard error of the difference of the two groups showed slight statistical significance at a level of  $t=0.05$ .

The raw data on ages are not precise, since many patients cannot date the time of onset. In such cases the age at the time of examination was taken; so this factor would tend to make the average age higher than it really is.

The semeiology of meralgia paresthetica is quite stereotyped, and the correct diagnosis can be safely inferred in most cases from the history alone. The patient describes a numb, burning, itching, or sometimes painful sensation over the thigh. The location is over the anterolateral aspect, being oftenest in the lower third of the thigh a few inches above the knee. The area of dysesthesia may range from a spot the size of a half-dollar to an elliptical patch encompassing the area from a few inches below the inguinal ligament to about 1 or 2 in. above the knee. This patch may be unilateral or bilateral. Of the 42 cases examined, 3 were bilateral.

The symptoms were intermittent, and the dysesthesia may have been present many years before neurological consultation was sought. It was usually no more than mod-

Fig. 1.—Age distribution of the 42 patients: 26 males and 16 females.





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erately distressing, and, to reiterate, in many the presence of meralgia paresthetica was coincidental to the prime reason for seeking neurological consultation.

As expected, in describing the dysesthesia, the patients were more or less articulate in communicating their sensory experiences. Common adjectives were "numbness," "burning," "crawling," "hot," "sensitive." Such descriptive accounts often were accompanied by a brief grimace, connoting a vague unpleasantness. In none of these patients were there the writhing, gasping, lip-biting demonstrations of agony, such as one customarily sees in facial neuralgia, glossopharyngeal neuralgia, causalgia, etc. Standing or walking made the distress worse in at least 11 patients.

Individual thresholds of pain and the presence of accompanying anxiety, of course, color the patient's response to the dysesthesia, but it appeared that the distress was not severe or disabling. Follow-up of these patients in retrospective discussions amply confirmed this impression.

I have observed a phenomenon that is characteristic of this disorder. Even before the medical history is obtained, while the patient's name, address, age, etc., is being recorded, the patient may be seen to sit forward in the chair, flex the trunk slightly to give freer play to his shoulder, and gently massage the anterolateral aspect of the thigh just above the knee. At this point, the examiner may anticipate the patient and summarize inform him what his symptoms are and what his diagnosis is. This deliberate display of clinical perspicacity may impress the patient sufficiently with the doctor's authoritative knowledge of his disorder that he will be responsive to the forthcoming assurance that meralgia paresthetica is benign.

Many patients, on direct questioning, reported that they "found" themselves pawing or rubbing the affected area in an automatic manner, much as one may compulsively thrust the tongue into a dental cavity or defect. Many claimed that they obtained temporary relief from the pain or

paresthesia by this laying on of hands. This might account for the depilation reported by some as evidence of trophic disturbance.

The neurological examination often reveals no objective zone of hypesthesia or hypalgesia, even though the area of dysesthesia is extensive. The zone of objective sensory loss may be one-tenth or less the size of the patch of dysesthesia. In nearly all cases in which objective sensory defect was present, the zone of subjective disturbance was much larger. The absence of objective sensory changes does not preclude the diagnosis.

Aside from the sensory involvement, the neurological examination is negative. As noted, there are no motor or reflex abnormalities. Trophic disturbances, for example, loss of hair, shiny skin, etc., have been described by others, but I have not observed any.

A representative case is selected to typify the syndrome.

A 17-year-old girl had been referred to the Group Health Clinic for neurological consultation four years previously because of lapses of consciousness. A diagnosis of convulsive disorder was supported by an abnormal electroencephalogram. She had been examined at regular intervals from then on. During a periodic neurological examination, the patient reported that two months earlier she had waked up with numbness and a pins-and-needles feeling over the anterolateral aspect of the left thigh. This area felt warm to her touch. The neurological examination showed marked hyperalgesia in an elliptical zone over the lower left thigh (Fig. 2). The rest of the neurological examination was negative. Aside from the aforementioned disorders, the patient had been in good health. A record of her development and physical examinations had been

Fig. 2.—Elliptical "snow-shoe" pattern of hypalgesia; no alopecia or other trophic disturbance.



made since she was 8 years of age. Appendectomy was performed in 1953.

The meralgia paresthetica varied in intensity but so far has persisted without causing any serious distress or discomfort.

This case demonstrates that meralgia paresthetica can occur in youth, and also epitomizes the typical unprovoked, unexplained, spontaneous appearance of the syndrome in an essentially healthy person. The pattern of sensory involvement without motor defect is characteristic. No depilation or trophic disturbance occurred at any time (Fig. 2). No treatment was necessary, and the patient rarely referred to it throughout the ensuing office visits, which were made because of the convulsive disorder.

The persistence of the paresthesia is typical.

This case also demonstrates the discovery of meralgia paresthetica in a patient more or less through inadvertence, as was done in many instances in this series.

The diagnosis of meralgia paresthetica implies an uncomplicated and isolated affection of the lateral femoral cutaneous nerve. The majority of cases of meralgia paresthetica conform to this specification and therefore constitute what may be called a primary, essential, or idiopathic meralgia paresthetica. But secondary meralgia paresthetica can occur, although rarely, due to affection of the nerve anywhere in its route. Primary causes of meralgia paresthetica must be sought for in every case before the inference is made that it is a classical, primary, or idiopathic meralgia paresthetica. It would probably be safer semantic practice to restrict the term "meralgia paresthetica" to the primary neuropathy and to use the term "lateral femoral cutaneous neuropathy" for the symptomatic, or secondary, cases. Some of the differences of opinion as to the causation of meralgia paresthetica stem from the failure to distinguish the two etiological types.

Even though the sensory pattern is stereotyped and the diagnosis simple, the patient requires a complete neurological examination. Further, in a few cases, additional,

and often elaborate, medical studies, including pelvic and rectal examinations, may be necessary. This is true especially if (1) there is a history of pelvic or abdominal disease, (2) there are other neurological signs and symptoms, or (3) the area of objective or subjective sensory disturbance extends beyond the well-defined limits of distribution of the lateral femoral cutaneous nerve. This last condition is particularly important; such a finding should create a strong suspicion that the patient does not have classical meralgia paresthetica. An example follows.

A 35-year-old secretary, seen at Group Health Clinic, developed numbness, burning, and itching over the anterolateral aspect of the left thigh. She often rubbed and scratched this area to obtain temporary relief.

Neurological examination revealed hypalgesia over the anterolateral aspect of the thigh on the left, the zone of objective and sensory disturbance extending several inches below the knee (Fig. 3). The left quadriceps reflex was more exaggerated. An uneasy diagnosis of meralgia paresthetica was entertained, but further studies, including spinal fluid examination, roentgenography of the spine, pelvic examination, and repeat neurological examination, were arranged. Signs and symptoms remained static for several months before a typical pattern of multiple sclerosis evolved, including anisocoria, esophoria, nystagmus, visual field defects, paresthesias of the face, dysgeusia, anosmia, absence of abdominal reflexes,

Fig. 3.—Zone of hypalgesia over anterolateral aspect of thigh, but exceeding area of distribution of lateral femoral cutaneous nerve. Diagnosis: multiple sclerosis.





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bilateral ankle clonus, etc. After several months other evanescent signs were manifest, which over one and a half years eventually became static and minimal.

A diagnosis of meralgia paresthetica would have been in error in this case. It was suspect because the extent of the sensory disturbance exceeded the well-defined zone supplied by the lateral femoral cutaneous nerve. If follow-up neurological examination had not been made, the correct diagnosis would have been missed.

As stated, when the history or neurological findings do not conform to the classical pattern, notably, if the sensory involvement extends beyond the lateral femoral cutaneous distribution, the practitioner is justified in pursuing a vigorous diagnostic program, including pelvic and rectal examination, gastrointestinal x-ray studies, and spinal fluid examination. The last is needed to rule out tabes or cord neoplasm.

Incomplete neurological examinations may be another source of confusion and disagreement. Rosenheck's uncritical report of osteoarthritis of the spine as a cause of meralgia paresthetica suggests such a possibility. Another author reports a case of meralgia paresthetica associated with the decreased quadriceps reflex and with atrophy of the thigh muscle.<sup>7,50</sup> Some of the case reports in the older literature suggest failure to distinguish meralgia paresthetica from protruded lumbar disc. The latter syndrome is, of course, much better understood and recognized today. X-ray examination of the lumbosacral vertebrae, particularly for multiple upper lumbar disc, Paget's disease, and metastatic lesions, tuberculosis, or other bone-destroying processes, should be made in suspicious cases. Myelography may be required. The following case is probably an instance of secondary meralgia paresthetica which apparently was a mere segment of progressing lumbosacral disease.

A 30-year-old man had had intermittent pain in the back and legs, which made walking and driving his car increasingly difficult. On diagnosis of arthritis, cortisone was administered. One year later he complained of tenderness over the right



Fig. 4.—Area of sensory defect in patient with reticulum-cell sarcoma.

iliac crest. Hysteria was suspected. Neurological consultation was sought.

In addition to a patch of hypesthesia over the anterior lateral aspect of the thigh on the right (Fig. 4), weakness of both legs and bilateral ankle and patellar clonus were found. There was tenderness to light percussion over the lumbosacral region of the spine, and pain in the lumbar area could be relieved by flexing the patient's knee.

A diagnosis of intraspinal mass, either granuloma or neoplasm, was made. Further studies at Veterans Administration, Mount Alto Hospital established the latter. Biopsy showed reticulum-cell sarcoma.

The following quite unusual case is probably best classified as secondary, rather than as primary or essential, meralgia paresthetica:

The patient, a boy, was only 10 years old. He had had sudden onset of pain in the right thigh and right buttock when he attempted to straddle his bicycle. The pain prevented this, and he limped home, getting temporary respite from the pain by resting on the way. The pain subsided both in the buttock and the thigh, but numbness developed over the anterolateral aspect of the thigh. A neurological examination was done two days later at Group Health Clinic, where a typical oval zone of paresthesia, about 10 times as extensive as the zone of hypalgesia and hypesthesia, was described. The patient stated; "It feels like your face after the dentist has injected Novo-



Fig. 5.—Zone of objective sensory deficit (crossed-hatched area) in 10-year-old boy. Dysesthesia was present in larger zone.

caine." There was no reflex or motor abnormality, no trophic disturbance, and no tenderness over the iliac crest or inguinal ligament. There was tenderness to light percussion over the first lumbar vertebra (Fig. 5).

Because of the concomitant pain in the right buttock, it was inferred that the posterior, as well as the anterior, branch of the lateral femoral cutaneous nerve was implicated at or near the root, probably associated with radiculitis. No skin lesion was present, but incipient herpes was suspected. The eruption appeared five days later.

It is apparent from this study that meralgia paresthetica is a common neurological disorder. It may occur by chance and unrelated to the neurological complaint that motivated the patient to seek medical examination.

One may deduce also that meralgia paresthetica can occur together with another neurological disorder but is only infrequently due to it.

Protruded lumbar disc was the most frequent disorder coexisting with meralgia paresthetica. 1. This might reflect the high relative incidence of protruded lumbar disc. 2. Protruded lumbar disc may be a cause of meralgia paresthetica. 3. The two may

have a common genesis. The higher proportion of men in this and in other series would weight the data, since protruded disc also occurs oftener in men. But, again, the relatively high incidence in the male permits no inference regarding cause and effect. Trauma could be the common denominator, but its precise mode of causation is obscure. In two patients there is clear history suggesting trauma.

One was a physician who at the age of 27 was kneed in the thigh by an opponent while jumping for a basketball. Pain and paresthesias appeared at once and persisted over the next 12 years. The disorder was never disabling, nor was it influenced by the subsequent development of a protruded lumbar disc, or by diverticulitis, which was successfully treated by surgery. When he wore a rigid back support which extended to the iliac crest, the meralgia paresthetica was intensified and the belt was discarded.

Another physician, age 42, examined because of protruded lumbar disc, was found to have meralgia paresthetica that had begun 18 years earlier. He was hanging onto a strap in a crowded subway car, holding a bag of groceries in the other arm, when a sudden stop caused him to pivot on the strap, rotating his trunk sharply. A sudden, burning pain was felt, as though hot water had been spilled over the thigh. The meralgia paresthetica has persisted, never troublesome and not influenced by the protruded lumbar disc, which has caused intermittent, brief disability. It is possible, of course, that the apparent trauma in these two cases could have precipitated the meralgia paresthetica in an already susceptible lateral cutaneous nerve.

In neither instance did the meralgia paresthetica follow the use of a back support or other device customarily employed in the treatment of protruded lumbar disc, as suggested by Ecker,<sup>49</sup> who found that 22% of his 150 patients had sciatica or other pain in the hip or back. A dozen of his patients who suffered from low-back or sciatic pain also had meralgia paresthetica, the onset of which occurred after the use of adhesive strapping or of a sacroiliac belt. He concludes that in association with sciatica, as elsewhere, meralgia paresthetica is caused by pressure or tension on the lateral femoral cutaneous nerve.

In only two of the nine patients with coexisting protruded lumbar disc in this series could this mechanism be suspected.

### Etiology

The confused, chaotic, and contradictory literature on the etiology of meralgia paresthetica affords many egregious examples of *non sequitur*, recondite inferences, and uncritical analysis. No unitary theory of causation is currently universally accepted.

In the 60 years that meralgia paresthetica has been recognized as an entity, an impressive list of alleged etiological factors has accumulated, many bizarre and implausible, including some suggested in the more recent literature. As in other ill-understood syndromes, this implies that the cause in most cases is unknown.

Wartenberg<sup>51</sup> expressed the opinion that nothing definite can be said at present about the etiology of this puzzling disease. He suggested that an obscure metabolic disturbance or, more likely, a toxi-infectious process might be responsible.

It is best to assume that we are dealing here with a specific or nonspecific reaction to a neurotropic virus of exceedingly low virulence with exclusive affinity for the sensory nerves. Such a virus infection may involve the peripheral nervous system as it occurs in the peripheral form of encephalitis epidemica and poliomyelitis.

Huddleson<sup>52,53</sup> expressed the belief that, in addition to peripheral neuropathy, meralgia paresthetica could result from a lesion of the dorsal root or its ganglion, or within the dorsal horn. He gave syringomyelia as an example.

Over 80 alleged causes were culled from the literature. Many causes are picturesque but have little else to commend them. Some deserve further comment, particularly those observations that suggest mechanical forces affecting the lateral femoral cutaneous nerve at or near the inguinal ligament or iliac crest. These appear most frequently in the literature.

Pal,<sup>54</sup> Fischer and Krieg,<sup>55</sup> and Miller<sup>30</sup> emphasize the role of imbalance of foot mechanics as responsible for meralgia paresthetica.

Presumably, the fascia lata is stretched or is made tense, and the nerve, as it emerges, is compressed. Musser and Sailer<sup>17</sup> and Stookey<sup>55</sup> disputed this theory. Stookey traced the nerve in the fascial canal of the fascia lata and found the nerve was not compressed by movements of the leg in extension or in flexion. He also concluded that the nerve is adequately protected by the arcuate arrangement of the fascial fibers and that the same was true at the points of emergence where the nerve branches passed through the fascia lata.

Stookey believed he found a more acceptable explanation in the marked angulation of the nerve as it emerges from the pelvis medial to the anterior superior iliac spine. He found that the nerve at this point forms an abrupt angle, which is considerably increased by extension and lessened by flexion of the thigh. He found other variations that might account for susceptibility to meralgia paresthetica, including passage of the nerve over the crest of the ilium immediately lateral to the anterior superior spine. Other variations were found in the area of the sartorius muscle. He concluded that the mechanism of meralgia paresthetica was repeated movements of a sharply angulated nerve as it leaves the pelvis, with continued trauma to the nerve in the movements of the thigh, especially in standing and walking. He believed that this mechanism was identical with that causing other neuritis, for example, late ulnar palsy, palsies due to cervical rib, etc.

Others have emphasized this mechanical type of attrition on the lateral femoral cutaneous nerve as responsible for meralgia paresthetica.<sup>39,41,56,57</sup> Mack<sup>39</sup> gave a vivid description of this phenomenon. While transplanting the lateral femoral cutaneous nerve in a prepared osteoplastic slot in the crest of the ilium, as described by Lee,<sup>58,59</sup> in 1941, he observed that the nerve was considerably thinned at the point of crossing the brim of the pelvis, which was also its point of emergence from the inguinal ligament. Coughing and straining produced an almost shutter-like action of the inguinal

ligament on the nerve at this point, and allegedly caused the thinning of the nerve. He sectioned part of the inguinal ligament.

Many of the proposed etiological hypotheses are difficult to correlate with the anatomy and function of the lateral femoral cutaneous nerve. It is quite possible that the patient, ill of some other, unrelated, and perhaps disabling, disorder, is inclined to reflect more on his soma and thus discover a previously subliminal sensory experience. Or, through the course of routine medical examination, a patch of hypesthesia is revealed, or the prone position in bed may have triggered this neuropathy. These possible explanations would be particularly likely in the disabling infections or in cases in which postoperative convalescence is prolonged; for example, several cases of meralgia paresthetica have been reported in typhus patients.<sup>2,11,59,60</sup>

The instance of meralgia paresthetica ascribed to *Trichinella* is of a different order, and probably is not representative. A thick, abnormally placed fibrous band due to multiple cysts of *Trichinella spiralis*, compressed a thin segment of a lateral femoral cutaneous nerve just below the iliac spine in one case reported by Cohen.<sup>61</sup>

Another curious involvement of the lateral femoral cutaneous nerve in its peripheral course was described by Kelly in 1944<sup>62</sup> in a 25-year-old soldier whose meralgia paresthetica was due to multiple nodular lipomata. Herpes zoster, according to Miller,<sup>36</sup> and serum sickness<sup>63</sup> are other lesions that may produce a secondary type of meralgia paresthetica.

Heredity has been blamed for some instances of meralgia paresthetica, and Mendel<sup>12</sup> compared the familial incidence of this disease to that of facial paralysis. He reported the case of a patient and the patient's father whom he treated for meralgia paresthetica. Näcke<sup>40</sup> is credited with being the first to describe the hereditary predisposition in meralgia paresthetica. Others have added instances,<sup>17</sup> including Goldstein,<sup>35</sup> whose cases have already been alluded to. Relevant to this question is a personal com-

munication from Sigmund Freud to Mendel: The Bernhardt disturbance which I described about myself some time ago has disappeared over the years without my trying to apply therapeutic measures. It may be interesting that one of my sons, at age 35 or 40, complained of the same minor condition, which his physician in Berlin suspected was a spinal disease.<sup>64</sup> Freud offered no further dynamic explanation and made no reference to his prior report, in which emotional factors were represented as a causative force.

### Anatomy of the Lateral Femoral Cutaneous Nerve of the Thigh

The precise mechanism of "neuritis" of the lateral femoral cutaneous nerve is generally accepted to be direct tension, compression, or pressure. This orthodox explanation was questioned by Kelly,<sup>64</sup> who presented arguments in favor of reflex effect of abnormal impulses which originate in the local nerve lesion following trauma and spread antidromically throughout the distribution of the nerve.

To determine what, if any, variations in the structure or organ relationships of the lateral femoral cutaneous nerve could be responsible for a subject's vulnerability to meralgia paresthetica, first-year medical school cadaver material was utilized. The course of the nerve was dissected and drawings made and reviewed with Prof. Othmar Solnitsky, of Georgetown University. This anatomical study was conducted over a period of two years, 24 cadavers being utilized in 1954 and 23 in 1955.

The suspicion that some anatomical variation in the lateral femoral cutaneous nerve might cause susceptibility has been expressed before. According to Musser and Sailer (1900), Brewer was the first to suggest, in a verbal communication to Freud, that the anatomical relations of the nerve to the surrounding structures "might have something to do with meralgia paresthetica, particularly on account of the superficial situation of the nerve and its exposure to injury."

Actually, this theory was proposed by Hager<sup>4</sup> in 1885, and by Osler in 1897.<sup>65</sup>

Roth contended that only in those persons in whom the nerve followed an abnormal course could meralgia paresthetica be produced. Tobias<sup>49</sup> and Stookey<sup>55</sup> have commented further on this possibility.

Anatomical texts and neurological treatises are uniform in their description of the course of the lateral femoral cutaneous nerve. It arises from the second and third lumbar roots. Infrequently fibers are contributed from the first lumbar root.<sup>66</sup> The fibers pass through and emerge from the lateral aspect of the psoas muscle, and then pass obliquely across the iliac muscle, maintaining a retroperitoneal position. The nerve runs beneath the cecum, appendix, and ascending colon, on the right side, before penetrating the inferior part of the inguinal ligament. A corresponding oblique course is pursued on the left side, where it lies beneath the sigmoid colon. It crosses the pelvic brim about 2.5 cm. medial to the anterior superior iliac spine. After passing through the inguinal ligament, it lies in apposition to the sartorius muscle, and 2 to 4 in. inferiorly it divides to supply the skin on the thigh, extending from the greater trochanter, above, to the knee, below.

In this study, attention was directed to five particular zones: (1) the root area; (2) the intra-abdominal and pelvic course; (3) the passage through the inguinal ligament; (4) the passage over the sartorius muscle, and (5) the course in the lower thigh.

A number of variations were observed. There was considerable inconsistency in the position in the psoas muscle. Most authorities say the nerve passes under the psoas muscle, but in many cases the nerve came through the belly of the muscle. It is conceivable that myositis or strain could compress the nerve at this site, but this is speculative. Gordon<sup>67</sup> attributed exacerbation of symptoms on standing to compression by the psoas muscle. In the pelvis the course was usually that described in the textbooks, but in five cadavers the nerve bifurcated in the pelvis, 1 to 4 cm. prior to penetrating the inguinal ligament. This variation has not been mentioned in the litera-

ture but in itself does not necessarily constitute evidence that the patient was more or less susceptible to neuropathy. Since the nerve in this variation passes through the inguinal ligament in two separate branches, the possibility is suggested that when surgery is done on this nerve, only the more lateral branch might be exposed, since these two branches are separated by 4 to 6 cm. at the level of Poupart's ligament (Fig. 6).

Most of the variations were found in the area of the inguinal ligament. Variations consisted of deviations from the typical position, which is about 1 in. below the anterior superior iliac spine. Some nerves were as much as 2 in. below; others were nearer. Some passed above the inguinal ligament; others ran beneath it. None of the specimens contained nerves that passed over the crest of the ilium lateral to the anterior superior iliac spine, as mentioned by Corlette.<sup>31</sup>

A large number of variations were observed where the nerve is in proximity to the sartorius muscle origin. At this site there may be repeated branching; the nerve may pass under, over, or through the sartorius muscle. At this point the nerve is usually encased in thick fascia.

In the fifth zone, branching into a posterior and an anterior branch occurs at this point usually, but this branching may occur immediately after passing through or 2 to

Fig. 6.—Anatomical relationship of lateral femoral cutaneous nerve. Courtesy of Dr. O. Solnitsky.



4 in. below the inguinal ligament. A posterior branch, after penetrating the thick fascia, runs laterally and posteriorly to supply the skin over the gluteal region. About 4 in. below the inguinal ligament, the anterior branch pierces the deep fascia and descends as far down as the external surface of the patella, with multiple branching to supply the skin in this area (Fig. 6).

### Comment

As a result of this combined anatomical and clinical study, one receives these impressions:

1. There is a preponderance of cases of meralgia paresthetica with no plausible explanation as to causation.

2. Radicular involvement seems unlikely as a cause of isolated lateral femoral cutaneous neuropathy, since one should find subjective or objective evidence of implication of the other nerves stemming from the second and third lumbar segments. Cases of meralgia paresthetica have been attributed, however, to spondylitis deformans and protruded lumbar disc.<sup>50,68</sup>

3. Injury or disease is likely to occur much more frequently beyond than within the spinal root area. Two sites of nerve damage seem likely:

(a) The passage of the nerves through the inguinal ligament at or near the iliac crest seems to be a likely, though, again, not a proved, site of compression or damage. The literature offers many instances of direct compression in this area. For example, one of Bernhardt's patients developed meralgia paresthetica after carrying a sword strapped to his side; a tight corset immediately caused the syndrome according to Lievre and Bloch-Michel.<sup>11</sup> Trusses and belts have been implicated by many authors.<sup>17,30,35,69</sup>

(b) The long, "exposed" course in the abdomen seems likely to render the lateral femoral cutaneous nerve susceptible to compression, irritation, or destruction, notably by neoplasm or infection, especially by the commoner intra-abdominal or pelvic

disorders. More scrutiny of this syndrome by non-neurological specialists might be enlightening. The literature on this aspect is not substantial but provides enough inferential evidence to encourage interest. The reward might be a practical sign of intra-abdominal disease. This idea is not new and has been reiterated by many writers. However, Obarrio and Guilhe,<sup>70</sup> in 1949, made the categorical claim, "We have the honor to be the first to have found the cause of 'essential' neuritis of the femoral cutaneous nerve; that cause is enteroptosis." In a prior communication in 1946,<sup>71</sup> they reported six cases with spastic colitis, ptosis of the transverse colon, visceroptosis, and pendulous abdomen. Mendel,<sup>12</sup> in 1933, in summarizing and analyzing the possible etiology, stated: "The pressure may also originate from the intestine, the gravid uterus, and intra-abdominal inflammations." Attention was also directed by Musser and Sailer<sup>17</sup> to the potential involvement of the lateral femoral cutaneous nerve in its abdominal course. Specific instances were recorded by Warda,<sup>72</sup> whose patient developed meralgia paresthetica after an ice bag had been applied to the right lower quadrant because of appendicitis; three cases occurred after appendectomy, according to Sittig<sup>73</sup>; another patient with appendicitis is reported by Schneck<sup>28</sup> and Schewket.<sup>74</sup> Corlette<sup>31</sup> added another case, and another of his patients developed meralgia paresthetica after a cholecystectomy. Brisard<sup>16</sup> added a case due to a uterine fibroid. A rapid abdominal enlargement due to cirrhosis and ascites was associated with meralgia paresthetica<sup>19</sup>; a left-sided ureteral calculus was associated with left meralgia paresthetica<sup>30</sup>; the latter promptly and completely subsided with the passage of the stone. Two cases of aneurysm of the abdominal aorta with meralgia paresthetica were found by de Castro,<sup>75</sup> who believes this former condition should always be considered as a possible cause of meralgia paresthetica. Lapinsky<sup>76</sup> insisted that meralgia paresthetica is not an independent



## MERALGIA PARESTHETICA

disease but is always a secondary projection of an irritative phenomenon, emanating from the abdomen or pelvis.

The occasional association of abdominal surgery and meralgia paresthetica suggests that direct trauma to the nerve during traction or manipulation may also be a causative factor, rather than the preexisting disease process that originally necessitated the surgery. An analogous event has been observed<sup>77-79</sup> with postoperative or postpartum evidence of damage to the femoral nerve. Maintaining a fixed position on the operating table or in the bed after surgery may play a part. Ecker and Woltman<sup>19</sup> collected 10 cases, 8 of which had no meralgia paresthetica until after surgery. The operations included a nephrectomy, in two cases; appendectomy, in two cases; exploration for a duodenal ulcer, in 2 cases; a herniorrhaphy for diaphragmatic hernia; a cholecystectomy; hyperrectomy, and radical mastectomy. It is difficult to explain direct nerve damage in the last operation. Bonica<sup>43</sup> described an unusual chain of circumstances in the case of a physician with meralgia paresthetica due to diverticulitis.

Of special interest, in regard to intra-abdominal alterations or disease, is pregnancy as an alleged cause of meralgia paresthetica. Again, an invalid claim of priority<sup>80</sup> is made in an article in which only two references are quoted. "Accounts of this condition during pregnancy has not, in the past, been pointed out." Bernhardt, whose original article included case histories only of men, stated, however, that he did not doubt that it occurred in women. Subsequently he described a patient in her seventh month of pregnancy. Others observed and commented on the correspondence of meralgia paresthetica and pregnancy, including Price,<sup>82</sup> Mendel,<sup>12</sup> Thebaut,<sup>83</sup> Rutherford,<sup>84</sup> and Viets.<sup>22</sup> Musser and Sailer reported on six patients during pregnancy. Ecker and Woltman<sup>19</sup> stated that the pregnancy is occasionally associated with meralgia paresthetica but probably exerts its effect by tension on the abdominal fascia



Fig. 7.—Area of hypesthesia precipitated by pregnancy, made worse by standing or walking.

rather than by direct pressure on the nerve in the abdomen. Lee,<sup>58</sup> in 1936, described a 22-year-old patient in whom an abortion had to be done because of severe pain due to meralgia paresthetica. Her third pregnancy was similarly terminated because of a recurrence of such pain.

Meralgia paresthetica began during pregnancy in four of my cases, one at the sixth month of an ectopic gestation. A 26-year-old patient was well until the fifth month of pregnancy, when pain suddenly appeared "just like boiling or very cold water was poured over my thigh." Numbness also was present at times. Another patient, age 34, was referred for neurological consultation because of protruded lumbar disc. In the course of the examination, meralgia paresthetica was found on the right side. History disclosed that mild itching and numbness, associated with hypersensitivity to touch, appeared during the third month of pregnancy. The sensory disturbance receded, but a relapse occurred during an ensuing pregnancy.

In two of the four pregnant patients the paresthesia was exacerbated by standing or walking (Fig. 7).

### Pathology

The presence of anatomical or pathological alterations of the nerve is uncertain.

Only rarely have gross alterations been observed at operation or at autopsy. Some have already been cited. The first recorded observation by Nawratzki<sup>85</sup> was a post-mortem examination of an 81-year-old man who had had meralgia paresthetica a spindle-shaped swelling of the nerve was found adjacent to the anterior superior iliac spines, and microscopic changes consisting of perineuritis and interstitial neuritis were confined to this area. Warda<sup>72</sup> and Stookey<sup>86</sup> also found local enlargement by gross examination. In contrast, an area of local thinning was found, as noted, by others. Extensive degeneration was found in the excised segment by Durarte.<sup>86</sup> Bramwell<sup>87</sup> found the nerve grossly and microscopically normal.

In King's<sup>20</sup> four female patients the nerves examined at operation were normal. In one alcoholic man, microscopic examination showed degeneration with shrinkage and separation of nerve fibers. Where it pierced the fascia lata, local interstitial edema was present. Axis cylinders could not be identified, and the nerve fibers were reduced to nucleated neurilemma cells.

### Treatment

Treatment is as varied, and often as unscientific, as many of the alleged causes. In many instances the recommended therapy reflects the author's particular etiological bias. In general, the therapeutic recommendations can be separated into surgical and nonsurgical. Many have accepted the dictum enunciated by Brain<sup>34</sup>: "The disorder usually requires operation." Others take a more moderate position. Ecker and Woltman state that for most patients no treatment is required, but add that resection of the nerve is now the standard operation for intractable cases.

Therapeutic orientation can be further classified as follows:

1. Conservative, that is, a complete laissez-faire management, aside from removing possible offending garments, trusses, belts, braces, etc.

### 2. Medical

- (a) Oral or parenteral drugs, for example, thiamine, antihistaminics have been used.

- (b) Injection of the nerve with cocaine, alcohol, or antipyrine has been suggested. Reichert<sup>23</sup> observed that the symptoms of meralgia paresthetica were similar to those of causalgia, which is due to irritation of the sympathetic fibers. Consequently, he used alcohol and procaine to obtain a sympathetic block by paravertebral injection of the lumbar sympathetic chain. His results were not impressive.

### 3. Physical

Massage, electricity, and heat, including wrapping the limb in flannel, have been recommended.<sup>88</sup> Hot sulfur baths, followed by use of ultraviolet light, support to the abdomen, and other physical measures, have been employed.

### 4. Surgical

Prior reference has been made to surgical measures. King<sup>20</sup> recommended conservative treatment unless the objective sensory findings are present and persist. In five patients the lateral femoral cutaneous nerve was sectioned in the upper thigh as it pierced the fascia lata to become superficial. He stated that this operation is the simplest and most satisfactory way in which to treat meralgia paresthetica which has proved resistant to conservative treatment. In the Ecker and Woltman series, when the symptoms demanded active treatment, resection of the nerve or neurolysis was advised. In contrast to King's operation, the procedure is performed at the site recommended by Stookey, rather than at a lower point.

As noted previously, Stookey sections the nerve at the exit of the pelvis but without excision. The nerve ends are left in alignment to encourage spontaneous regeneration and subsequent nerve lengthening.

Still another procedure "is designed to obviate the pincer-like action on the nerve at the outer end of Poupart's ligament, by dividing one or the other of the 'blades' of the pincers" (Learmonth<sup>36</sup>). He made a



small incision below each anterior superior iliac spine. Both nerves were found to be thickened, reddened, and indented by the upper pillars of Poupart's ligament. The upper pillar was divided on both sides, and the deep fascia of the thigh also was split up. The nerves were mobilized but not sectioned.

A variation of this operation was performed by Lee in 1936.<sup>58</sup> The nerve was located in the fibrous canal immediately below the inguinal ligament and found to be one-third the size of the nerve in the thigh. A small portion of the fibrous origin of the internal abdominal oblique muscle was sectioned, and the entire circumference of the nerve was freed. Several days later the pain was relieved but returned after two and one-half months. Lee expressed the hope that a modified neurolysis operation might supplant the generally accepted method resection. Subsequently, in 1941 Lee<sup>60</sup> described such a modification, which attempts not only to relieve the patient of his pain but also to restore normal sensation in the involved area. Pressure and tension, the alleged causes of meralgia paresthetica, are relieved by relocating the nerve in the slot prepared in the ilium.

Surgery is not always successful. In Fulton's biography of Harvey Cushing<sup>60</sup> a vivid account is given of an "embarrassing" incident in connection with surgery for meralgia paresthetica. Cushing, in 1900, operated on the famous astrophysicist Simon Newcomb for this condition. "His operation went well enough . . . though the old gentleman was somewhat abominous. He insisted on propping himself up on his elbows every now and then to see what we were doing, but unfortunately his centre of gravity intervened." The patient kept up a running conversation during the procedure and was elated over the immediate relief of pain. Since Cushing refused to accept a fee, the patient, bursting with gratitude, naively called a press conference asking the reporters to print the wonderful news of his cure. This they promptly did, with

pictures, in a vivid and garish manner. "It was long before we lived it down." The pain recurred, and Finney reoperated, without success.

Even when pain is relieved, the consequent numbness may be just as annoying as the original dysesthesia. The 42 cases reported here were not subjected to surgery in any instance. Even the few more distressed patients were advised against it. All patients, after reassurance, preferred to live with the dysesthesia. No drugs were necessary. As stated, the physician performs an important, and usually lasting, therapeutic step when, after a careful examination, he categorically states the benign nature of the affliction. No patient has returned because of anxiety or distress over the dysesthesias. To determine whether they went elsewhere for more definitive treatment, 10 Group Health patients were sampled. Since these patients are free to seek consultation without further charge, cost was not a deterrent. All are "living with the symptoms."

### Prognosis

In this series, as in others, the disease varies in duration and is subject to spontaneous cure and to intermittent recurrence, usually for no apparent reason. It usually persists, with sporadic exacerbations, for many years. Ecker and Woltman concluded from their study that when the symptoms have lasted less than two years, the chances are 2:1 that they will disappear spontaneously within another two years. The duration of one case reported by Curschmann<sup>49</sup> was 46 years.

Gowers summed up the patients' prospects by saying that the disease "seems to have no sinister significance but has little tendency to yield to treatment."

### Summary

This analysis of meralgia paresthetica was undertaken to arrive at a sharper definition of the clinical syndrome, to determine its incidence, pattern, and prognosis, and to try to reconcile the varied, and often

extreme, notions on causation and treatment. A review and critical appraisal of the literature was attempted.

Dissection of the lateral femoral cutaneous nerve of the thigh in 47 cadavers revealed multiple variations, but none that would necessarily cause vulnerability to meralgia paresthetica.

Forty-two patients with meralgia paresthetica, encountered over a period of seven years, are reported. Only 16 were referred for neurological examination, primarily for sensory defects involving the thigh. In the other 28 the disease was discovered by making specific inquiry into the presence of dysesthesia of the thigh and by directing the sensory examination to this area. The sampling situation is further outlined and statistical analysis presented. The patient with meralgia paresthetica may be seen first by the general practitioner, internist, orthopedist, obstetrician, or surgeon.

It was inferred that meralgia paresthetica is common, that it can occur through a wide range of ages, and that it is almost always benign, and rarely due to sinister disease. However, a careful neurological, and often intensive physical, examination is required to rule out causes other than nonspecific neuritis, e. g., neoplastic or degenerative disease. Examples are cited. The diagnosis of idiopathic meralgia paresthetica should be suspected (1) if the area of objective or subjective sensory defect exceeds the well-circumscribed area of distribution of the lateral femoral cutaneous nerve; (2) if other neurological signs or symptoms co-exist, and (3) if there is a history of intra-abdominal disease. The last has been known to implicate the nerve, and this may be a manifestation of intra-abdominal or intra-pelvic disease.

A wide variety of alleged or assumed causes for meralgia paresthetica was culled from the literature. No unitary explanation is universally accepted.

Treatment in this series consisted exclusively of laissez-faire management. The benign nature of the mononeuritis was explained and the patient categorically re-

assured. Contrary to the recommendation of many authors, surgery was not advised. Follow-up examinations of the patients with classical meralgia paresthetica justifies this position.

The prognosis varied, but in most the dysesthesia persisted, being often intermittent, and occasionally precipitated by standing, walking, or pregnancy. It was rarely distressing or disabling.

Dr. Robert Wartenberg made many valuable criticisms and suggestions, in addition to loaning me his collection of reprints. Miss M. J. Adamson, librarian at the Veterans Administration Hospital, Mount Alto, W. Va., was an energetic and resourceful collaborator, who obtained most of the books and journals. Mrs. Orlando Caciola prepared the charts, and Mr. Victor Landi made the photographs. Dr. Othmar Solnitsky, professor of anatomy at Georgetown University, loaned me his collection of reprints and devoted much time in helping me with the anatomical study. Mrs. Kate Loewe helped with the translations.

1801 K. St. N. W. (6).

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# Chronic Respiratory Acidosis Due to Brain Disease

## *Reversal of Normal Electroencephalographic Response to Hyperventilation*

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### I. Introduction

In recent years attention has been directed to the alteration in the chemical constituents of the extracellular fluid resulting from cerebral lesions other than those located in the hypophysis. It is the purpose of this communication to report yet another type of metabolic abnormality—chronic respiratory acidosis—due to disease of the central nervous system.

The effect of cerebral lesions on the excretion of sodium and chloride ions was first reported by Allott<sup>1</sup> in 1939. The syndrome which he described consists of severe hypernatremia and hyperchloremia associated with moderate azotemia, hyperchloruria, and hypopotassemia in a patient without dehydration. Other reports of similar nature have been published by MacCarty and Cooper,<sup>2</sup> Sweet et al.,<sup>3</sup> and McLardy.<sup>4</sup> It seems likely that this chemical pattern results from damage to the hypothalamic nuclei in the distribution of the anterior cerebral arteries. There are many reports of sodium and chloride disturbances resulting from lesions in the region of the suprapontic and other hypothalamic nuclei in both animals and man.

Although there has been great physiological interest in the neural organization, localization, and sensitivity of the respira-

tory "centers," the function of which is to regulate the excretion of large quantities of acid, there has been only one previous clinical report<sup>5</sup> of abnormalities in the excretion of carbon dioxide as a result of lesions in these "higher centers."

It should be pointed out at this time that abnormalities of carbon dioxide excretion resulting from respiratory paralysis of the lower motor neuron type, such as is seen in bulbar poliomyelitis, will not be considered in this paper. Similarly, abnormalities of cerebral control of respiratory gases induced by drugs (barbiturates, gaseous anesthetics, salicylates, morphine, etc.) will be excluded from discussion.

Sarnoff, Whittenberger, and Affeldt<sup>5</sup> reported the case histories of four patients suffering from acute bulbar poliomyelitis who developed unusual respiratory abnormalities. In these early cases paralysis of the lower motor neuron had not developed; yet their breathing was irregular in rate, shallow, and exceedingly slow. It was striking that these patients were capable of breathing quite normally when commanded to do so by frequent and firm verbal orders. The retention of volitional control of respiration with the loss of the reflex, unconscious, rhythmic control appeared to those authors to be due to loss of sensitivity of the respiratory center to increased arterial carbon dioxide. The respiratory disturbances reported were all of an acute and transient nature, and electroencephalograms were not recorded. Some of the patients subsequently developed frank respiratory paralysis.

Many different types of respiratory abnormalities have been reported as compli-

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The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the view of the Navy Department or the Naval Service at large.

cations of epidemic encephalitis. This subject was most recently and thoroughly reviewed by Turner and Critchley,<sup>6</sup> who divided these disturbances into the acute and the chronic type. Among the abnormalities observed during the acute and early convalescent phases of this disease were tachypnea, with rates up to 100 per minute. Less commonly, brief periods of apnea were observed. They classified the chronic respiratory disorders under three main groups, although mixed forms were frequently observed: (a) disorders of respiratory rate (tachypnea, bradypnea); (b) dysrhythmias or disorders of respiratory rhythm (Cheyne-Stokes respiration, breath-holding spells, sighs, forced or noisy expiration, inversion of the inspiration-expiration ratio), and (c) respiratory "tics" (yawning, hiccough, spasmodic cough, sniffing).

One of the uncommonest respiratory abnormalities which followed the world-wide pandemic of epidemic encephalitis was bradypnea, which is mentioned only in passing in most reports, including the review by Turner and Critchley. Detailed studies of the pulmonary and the arterial gas concentrations have not been reported in these cases. Although electroencephalograms have been reported in many cases of encephalitis, they have not been recorded when this condition has been associated with a respiratory abnormality.

The following case presented a unique opportunity to study both the chemical and the electrical disturbances produced by a chronic abnormality in the function of the "respiratory center."

## II. Report of a Case

A 50-year-old white woman was referred to the neurology clinic at this Naval Hospital because of excessive somnolence.

In 1921, at the age of 17, she developed an extremely high fever, which persisted for 7-10 days, during which time she was delusional and hallucinated. She can barely recall the acute phase of this illness but vaguely remembers a stiff neck and muscle aching. During the three-week period that she remained in bed she slept most of the time, and, on returning to work, she would frequently

fall asleep while standing. On one occasion, about two months after returning to her work in a textile mill, she fell asleep and caught her hand in a machine. The somnolence gradually subsided over a three-month period, but she did not regain her usual state of health for six months. At the time the patient suffered from this illness there were several cases of acute epidemic encephalitis (encephalitis lethargica) reported to the public health authorities of her locality.<sup>7</sup>

In 1938 an appendectomy was performed. She did not regain consciousness for 24 hours after completion of the surgery and was said to have been cyanotic during this time. She was told she had developed atelectasis. The treatment consisted of oxygen administration, and a tracheotomy was performed. After she regained consciousness, recovery from the surgery was uneventful.

In 1940 she first began to experience episodes of excessive hunger and sleepiness, of several days' duration. These bouts of eating and sleeping would not recur for several months.

By 1946 she realized that she was sleeping excessively at all times. She would even fall asleep while entertaining friends. At the same time she was still eating excessively and had gained 40 lb. (18.1 kg.).

In 1947 she first sought medical attention because of occasional ankle edema and cyanosis of the lips. She was told that she had heart disease, but no therapy was given.

In 1949 her somnolence became worse, and she would sometimes fall because she had fallen asleep while standing or walking. Her appetite was still vigorous, but she did not gain any more weight. She spent many hours of her day dozing lightly.

She was first admitted to this Hospital in April, 1952, because of marked peripheral edema, which was not associated with exertional dyspnea, paroxysmal nocturnal dyspnea, or cough. She had a Grade 1-2, harsh, blowing systolic murmur in the pulmonic area and was noted to be slightly cyanotic while awake but markedly cyanotic when she slept. Her respiratory rate during sleep was reported as 6 per minute. There was no clubbing of the fingers or toes. The significant laboratory findings were as follows: circulation time and venous pressure, normal; hematocrit, 54%; RBC, 5,150,000; hemoglobin, 14.9 gm. per 100 cc.; protein-bound iodine, 4.1  $\mu$  per 100 cc. (normal);  $\text{CO}_2$  content, 60.2 vol.%; chloride, 91.5 mEq/L.; sodium, 147 mEq/L.; potassium, 5.25 mEq/L.; urine, alkaline; specific gravity, 1.015.

An electrocardiogram was consistent with right heart strain, and P-wave changes were suggestive of right auricular enlargement. Chest films showed minimal cardiac enlargement and a slight increase



in the bronchovascular markings with mild enlargement of the pulmonary conus.

Digitalis and mercurial diuretics were administered, and a marked diuresis followed. There was no change in the gaseous content of the blood or in the cyanosis of the lips. Although the diagnosis was then in doubt, the patient's symptoms referable to the edema had improved, and she was discharged.

The patient was readmitted two years later because of progressive somnolence. She had continued taking the digitalis but had found it unnecessary to continue the mercurial diuretic injections, as her ankle edema was no longer a problem. Results of physical examination in 1954 were unchanged, and her laboratory studies revealed a respiratory acidosis, with a  $p\text{CO}_2$  of 78 mm. Hg, a  $p\text{O}_2$  of 55 mm. Hg, an  $\text{O}_2$  saturation of 84%, and a pH of 7.22. It was again remarked that her cyanosis became more marked when she slept and that her respiratory rate was slowed during sleep. During this hospitalization, pulmonary function studies and cardiac catheterization were performed. The results of these two investigations will be separately discussed in the next section. The patient was placed on dextroamphetamine sulfate U.S.P. (Dexedrine sulfate) and achieved minor relief of her symptoms.

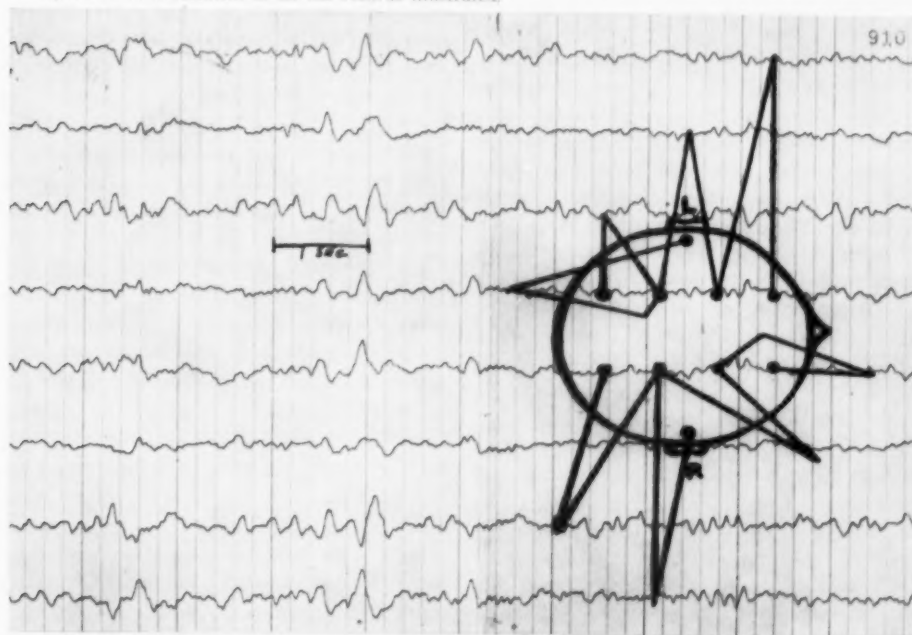
In 1955 the patient was referred for neurological consultation because of her continued complaint of somnolence despite dextroamphetamine therapy. Examination revealed a total absence of ocular convergence, with failure of the pupils to react on the attempted movement. They reacted briskly to light. The patient was oriented, but a careful history was difficult to elicit because she frequently fell asleep during the interrogation. The remainder of the neurological examination was normal except for a slight static tremor of the outstretched hands. This was rapid in rate and small in amplitude. It was not Parkinsonian in type. The patient denied having any other symptoms of Parkinsonism, and there was no rigidity of the muscles.

### III. Clinical Studies

Electroencephalography was first performed early in 1954 and was reported to show "a few runs of 6-7 cps activity of low voltage which were not noted during hyperventilation."

Electroencephalography was again performed as part of the neurological consultation in 1955, and at this time an unusual

Fig. 1.—Basal EEG with superimposed electrode-position guide. The channels in all the following EEG tracings represent identical electrode placements. A blood specimen was withdrawn at the time this record was taken (Table 1). Time scale is indicated on the first record and is identical in all the records illustrated.



reversal was observed in the response to hyperventilation. The basic frequency during "normal" ventilation was 6-7 cps in all areas in moderate to high voltage. Superimposed upon this rhythm, and at times completely replacing it, was a slow wave,

carbon dioxide retention resulted from central nervous system disease.

(a) *Cardiopulmonary Studies.*—The first pulmonary function studies performed on this patient, on May 14, 1952, revealed the following values:

	Amount	Per Cent of Predicted Value	Normal
Maximum breathing capacity	74 l/min.	90	80% or over
Vital capacity	2837 cc.	102	80% or over
Residual volume	654 cc.	77	Under 140%
Total lung volume	3491	96	80% or over
Alveolar nitrogen	1.33 vol. % (after 7 min. of 100% O <sub>2</sub> breathing)		2.5 vol. % or less
Arterial blood (at rest)			
Oxygen saturation	90.7%		96±2%
CO <sub>2</sub> content	57.0 vol. %		45±9 vol. %

varying in frequency between 2½ and 4 cps. There were also K complexes and synchronous slow waves of 1½ to 2 cps. The tracing superficially resembled those usually seen in adults in the sleeping state, but the patient, however, was definitely not asleep when the tracing (Fig. 1) was recorded. She did admit to mild drowsiness. Spindle activity in the 12-15 cps range was never seen under these conditions. On voluntary hyperventilation these abnormalities slowly cleared and the voltage declined appreciably. The basic frequency increased to 9-11 cps (Fig. 3), and fast activity was recorded from the frontal regions. An alpha rhythm slowly emerged and became present for prolonged periods of time. No waves below a frequency of 8 cps were recorded after the EEG had achieved its maximum change. After hyperventilation was discontinued, the record slowly reverted to its initial character. Similar improvements of EEG patterns during the hyperpneic phase of Cheyne-Stokes respiration have been recorded by Engel and Romano\* in four patients with cardiac decompensation.

These changes were thought to be consistent with carbon dioxide narcosis, and it was at first assumed that the carbon dioxide retention resulted from pulmonary or cardiac disease. The following special studies show, beyond any doubt, that this first assumption was incorrect, and that the

It was evident from these studies that there were oxygen desaturation and carbon dioxide retention in the arterial blood. However, the ventilatory studies and lung volumes failed to reveal any abnormalities to account for these chemical findings.

Further studies in 1954 gave similar findings except that the oxygen saturation was 89.4% and the carbon dioxide content was up to 64.88 vol. % from 57 vol. %. It may be noted that in 1954 more marked carbon dioxide retention was discovered, and this was associated with increasing complaints of somnolence.

Cardiac catheterization performed in 1954 revealed that the pulmonary artery pressure was 42/22 mm. Hg, with a mean pressure of 37.5 mm. Hg. (normal 30/16, and mean pressure 20 mm. or less). The right ventricular pressure was 43/6 mm. Hg (normal 30/6 mm.). Blood gas contents from the chambers of the right side of the heart were within normal limits and thus failed to reveal any evidence of a left-to-right shunt. At the time of the cardiac catheterization it was postulated that the marked hypoxia and hypercapnia could be due to one of six causes: (1) emphysema, (2) pulmonary fibrosis, (3) congenital heart disease, (4) primary pulmonary hypertension, (5) multiple small pulmonary infarctions, or, (6) central nervous system disease.



The pulmonary function studies proved that emphysema was not present. Congenital heart disease was also ruled out, as there was no evidence of a significant vascular shunt. Moreover, a congenital heart was unlikely, as it could not account for the carbon dioxide retention. Pulmonary fibrosis was excluded by x-ray studies; furthermore, it would not result in such hypercapnia. Primary pulmonary hypertension in the absence of a pulmonary ventilatory defect would not result in hypercapnia. The mild pulmonary hypertension recorded by catheter is probably due to the chronic hypoxia, the resulting high hematocrit of 58%, and an increased total blood volume of 5269 cc. (normal for weight is 3800-4300 cc. by the technique used). Multiple pulmonary infarctions were not considered likely in this patient. The remaining possibility, that of central nervous system pathology, was felt to be the most likely explanation for the

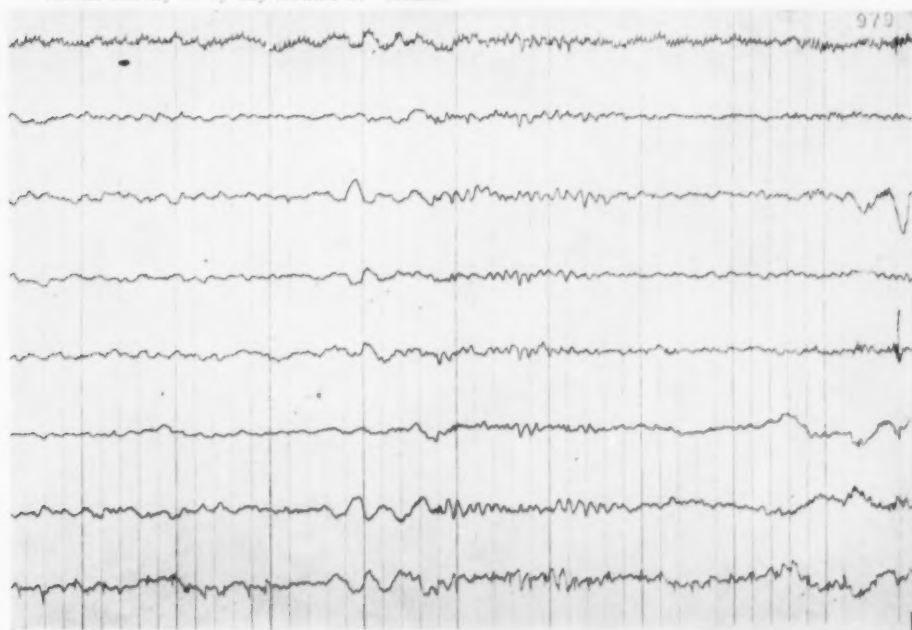
arterial blood gas abnormalities.

Repeated pulmonary ventilatory studies in 1955 again substantiated the earlier findings and were conclusive evidence that the hypercapnia and hypoxia could not be due to a pulmonary ventilatory defect. Indeed, at this time the patient's performance in these tests gave even more "normal" values than previously.

(b) *Combined EEG and Blood Gas Analysis.*—In view of the inability to explain the carbon dioxide retention on the basis of a cardiac or pulmonary lesion, further investigation of the relationship of the blood gases to the EEG changes was attempted.

An indwelling Cournand needle was placed in the right femoral artery so that blood could be withdrawn painlessly at any time during the EEG investigation. An electroencephalogram was recorded continuously on a Model III-D, eight-channel Grass electroencephalograph. Studies in this manner were performed prior to and during

Fig. 2.—EEG following six minutes of hyperventilation. The Figure illustrates the gradual disappearance of the delta activity, with return of alpha rhythm. The tracing demonstrates that the delta activity was not suddenly abolished by the act of concentrating on hyperventilation. There was no evidence that the delta activity could be abruptly abolished by any mental activity or by any method of "arousal."



a course of acetazolamide (Diamox; carbonic anhydrase inhibitor) therapy. As these studies were almost identical, only one will be reported. The sole difference between the two studies was the pH at the onset. Before acetazolamide the pH was 7.34, and it rose to 7.45 after nine and one-half minutes of hyperventilation. After acetazolamide was given, the pH was 7.21 and did not change significantly with hyperventilation, although the EEG response was unchanged.

After the patient had recovered from the minor discomfort and anxiety attending the surgical procedure and had returned to her usual, resting EEG pattern, the first blood specimen was obtained (Fig. 1 and Table 1). The expected hypercapnia and hypoxia were again recorded, with an associated pH of 7.21 (pH was 7.34 before acetazolamide). Hyperventilation was then begun and continued until the patient was exhausted and could no longer go on. That some slowing of the EEG was still present,

even after six minutes of hyperventilation, is illustrated in Figure 2.

After nine and one-half minutes of hyperventilation, the patient fatigued and "normal" ventilation was resumed. Figure 3 is typical of the normal EEG appearance at the end of the hyperventilation period, and in Table 1 the quantitative values of the blood gas contents are listed. The carbon dioxide content had been reduced to the upper limits of normal, and the oxygen saturation was at the lower limits of normal. It would be difficult to state categorically at this point which variation toward normal (the carbon dioxide or the oxygen saturation) was responsible for the normalization of the EEG.

Figure 4 shows the first reappearance of delta activity, 26 seconds after normal ventilation had been resumed. This low-voltage delta activity continued intermittently for the next four minutes. Three and a half minutes after normal ventilation had been resumed, a blood gas analysis revealed that

Fig. 3.—EEG at end of nine and one-half minutes of hyperventilation. This record is of the Harvard F-I type (slightly fast).



TABLE 1.—Relationship of Electroencephalogram to Blood Gases

Time	EEG, Fig. No.	Arterial Blood Gases—Whole Blood					Arterial pH
		CO <sub>2</sub> Content, Vol. %	O <sub>2</sub> Content, Vol. %	Satura- tion, %	CO <sub>2</sub> Tension, Mm. Hg	O <sub>2</sub> Tension, Mm. Hg	
Resting	1	62.08	17.20	90.8	72	71	7.21
After 6 min. hyperventilation	2	No blood sample					
After 9 1/2 min. hyperventilation	3	55.48	17.71	94.9	48	103	7.21
Time after normal ventilation resumed							
26 sec.	4	No blood sample					
3 1/2 min.	5	61.83	13.68	74.0	68	44	7.21
28 1/2 min.	6	63.16	14.48	75.3	75	46	7.17
				Over		Over	
After 9 1/2 min. of breathing 100% O <sub>2</sub> at normal ventilatory rate	7	65.32	19.92	100	75	100	7.18

the carbon dioxide had almost returned to its prehyperventilation level, while the oxygen saturation had fallen to an extremely low level of 74.0%. During the posthyperventilation phase the patient had marked bradypnea, and for a period was apneic. This is clearly the explanation for the fall in oxygen saturation. Yet the EEG, which is known to be sensitive both to changes of carbon dioxide content and, to a less extent, to the oxygen saturation of the blood, was less abnormal (Fig. 5) than in the control period (Fig. 1), when the oxygen saturation was more nearly normal.

Anoxia will produce some EEG slow waves only when the oxygen saturation is well below 60% and the CO<sub>2</sub> content is within normal limits. Gellhorn and Hailman<sup>9</sup> have shown that elevation of the arterial carbon dioxide level will "protect" cerebral function from the deleterious effects of anoxia. Similarly, the slowing of the EEG due to anoxia is reversed by increasing the level of CO<sub>2</sub>.

To determine which factor (hypercapnia or hypoxia) was the important one in altering the EEG, the patient was permitted to rest for 28 1/2 minutes and was then told

Fig. 4.—EEG 21 to 31 seconds after "normal" ventilation was resumed. The patient was apneic after this period. At the 26th second the first definite delta activity reappeared.

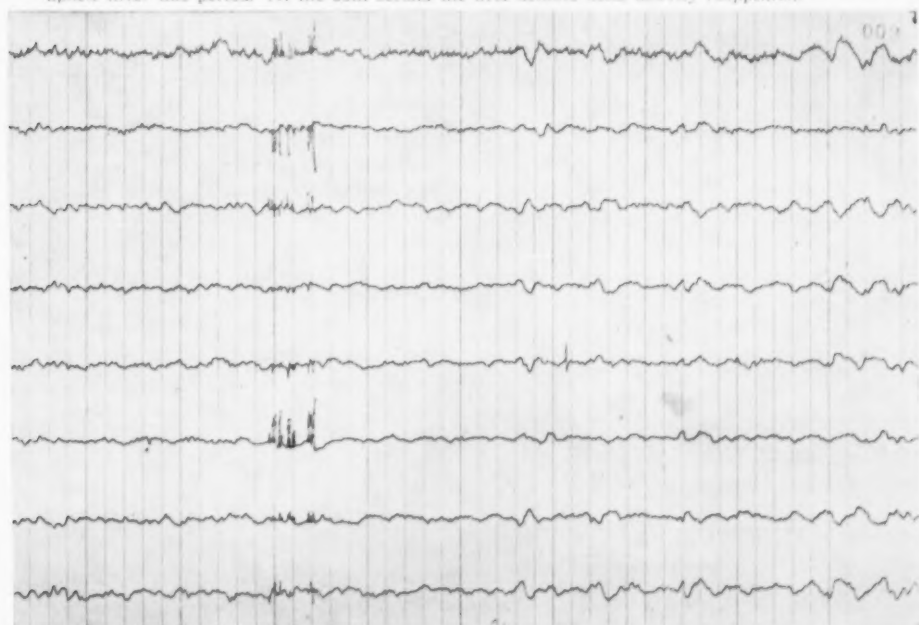




Fig. 5.—EEG three and one-half minutes after normal ventilation was resumed. The full delta activity has not yet returned as it was during the control period. Carbon dioxide content, too, had not yet fully returned to control level. Oxygen saturation is extremely low at this point, due to posthyperventilation bradypnea.

Fig. 6.—EEG 28½ minutes after "normal" ventilation was resumed, and immediately prior to the inhalation of 100% oxygen.





Fig. 7.—EEG nine and one-half minutes after breathing 100% oxygen at "normal" respiratory rate. The patient was awake and responsive to all commands during this recording but did feel drowsy.

to breathe 100% oxygen at an even, steady rate which was comfortable for her. This was continued for an equal length of time (nine and one-half minutes). Figures 6 and 7 demonstrate the two EEG patterns recorded, while Table 1 lists the chemical changes before and after oxygen breathing. During this phase of the experiment the patient was wide-awake and responded adequately to all commands. It was not possible to test slight alterations in consciousness, though she may have been slightly drowsy. Inspection of these figures indicates that the only significant change in the blood gas studies was in the level of oxygen saturation. This change from 75.3% to over 100% saturation was not effective in reducing the extent of the slow-wave activity. Indeed, Figure 7 has even more slow activity than Figure 6 (or any other tracing), and the  $\text{CO}_2$  content was at the highest level.

It can be concluded that EEG abnormalities in the first phase of this study were due to the effects of carbon dioxide retention and not to the mild hypoxia.

In Table 2 the EEG's are arranged not in chronological sequence but, rather, in terms of increasing amount of delta activity. Inspection of this Table shows the relationship of increased  $\text{CO}_2$  content to increased slow-wave activity and the absence of such a relationship to the degree of oxygen saturation. The same relationship between increasing  $\text{CO}_2$  content and delta-wave activity was found on a previous occasion when the same experiment was performed.

(c) *Psychic Correlations.*—It was generally noted that the patient was drowsy when the EEG was particularly slow. It was

TABLE 2.—Relationship of Slow-Wave Activity to  $\text{CO}_2$  Content and Oxygen Saturation

EEG (Fig.)	Carbon Dioxide Content, Vol. %	Oxygen Saturation, %
3	55.48	94.9
4	No blood sample	
5	61.82	74.0
2	No blood sample	
1	62.08	90.8
6	63.16	75.3
7	65.32	Over 100.0

sometimes necessary, to get a detailed history, for us to ask her to hyperventilate for a few minutes. After such a procedure the patient gave a more lucid account of her difficulties and tended to be less irrelevant. However, at other times, even when the  $p\text{CO}_2$  was quite high, she disclaimed drowsiness but complained of "fatigue." This tended to be unusual but was sometimes observed. It was repeatedly observed that she was awake, though perhaps drowsy, when her EEG pattern resembled those of normal sleep in other subjects. Speaking to her at these moments evoked a verbal response but no alteration of the slowing of the EEG. Thus, no "arousal" response could be elicited. When she was actually permitted to go to sleep, the EEG did not appreciably change except that spindle activity was then recorded, which was not previously present. Arousing her from true sleep caused a dispersal of the 14-cps-spindle activity. The slowing, however, persisted.

As there is no test that is sensitive to these subtle alterations from full wakefulness to slight drowsiness, it was difficult to be certain at any one moment of an absolute and rigid correlation between the EEG changes and her state of awareness. What tests do exist for such measurements are at best crude and are applicable only to more prolonged studies, but are not suitable for moment-to-moment evaluation, as would have been necessary in this patient.

(d) *Effect of Drugs.*—1. *Salicylates:* As a result of the previous observation, it was postulated that this disorder of the EEG and blood gases was due to a central nervous system insensitivity to carbon dioxide. It was therefore important to know whether this was an absolute insensitivity or whether the respiratory centers could be made more sensitive by the administration of salicylates.

The use of salicylates to modify the respiratory response to inhaled carbon dioxide has previously been reported by Alexander et al.<sup>10</sup> Acetylsalicylic acid in a dose of 3 gm. daily was given for seven days, and

arterial blood analysis was repeated. At the time of the second analysis the serum salicylate level was 2.5 mg. per 100 cc. There was no significant change in the blood gas concentrations as a result of this medication.

2. *Carbon Dioxide:* The patient was given a 7%  $\text{CO}_2$ -83%  $\text{O}_2$  mixture to breathe for 10 minutes, and no increase in ventilation was noted. Similarly, blood gas analyses following the addition of carbon dioxide to the inspired air revealed no change in the carbon dioxide content and only a slight increase in  $\text{CO}_2$  tension in the blood from 72 to 77 mm. Hg. This is evidence of the insensitivity of the respiratory center to carbon dioxide (in the concentration used)—the chemical known to be the most powerful in stimulating respiration and the chief stimulus to normal respiration.

3. *Caffeine Citrate:* The possible effects of a milder respiratory stimulant, caffeine citrate, were also studied. Five grains was given three times daily, with no improvement in her status or any change in the EEG pattern.

4. *Acetazoleamide:* This drug has been known to lower the plasma carbon dioxide concentrations (as well as the bicarbonate levels) in patients with carbon dioxide retention due to pulmonary emphysema. This drug is an inhibitor of carbonic anhydrase, the enzyme which in the kidney speeds the formation of carbonic acid from carbon dioxide and water.

Acetazoleamide was given in a dose of 250 mg. twice a day for a period of two weeks. The patient noted an increase in her symptoms of somnolence and fatigue while on this therapy. Arterial blood studies indicated that there was no change in the oxygen saturation. The carbon dioxide content of the arterial blood was increased up to 70.78 vol. %, from a previous level of 62.08 vol. %. In addition, the pH fell from 7.32 to 7.21.

From a theoretical point of view, we should not have expected any improvement on acetazoleamide, for it had been repeat-



edly demonstrated that the patient could move large quantities of air through her lungs. The locus of this patient's physiological disturbance is in the respiratory center and not in the lungs or kidneys.

Evidence that renal disease was probably not a factor in her condition came from repeatedly normal urinalyses, with concentrations of at least 1.018 on several specimens. There had never been any albumin, casts, or abnormal concentration of cells in the urine. Blood urea nitrogen determinations were always normal. Indeed, her compensated respiratory acidosis (before acetazolamide was given) with a  $\text{CO}_2$  of 62.08 vol. % and a pH of 7.32 also indicates an adequate capacity of her kidneys to excrete acid.

### Comment

A patient suffering from chronic respiratory acidosis has been studied. In addition to a low pH and hypercapnia, frank hypoxia has been demonstrated. The condition has persisted for at least 4 years and, it seems valid to assume, began about 10 years ago, when she first experienced chronic somnolence. Repeated pulmonary ventilation studies and cardiac catheterization have failed to disclose any abnormality of the cardiorespiratory system sufficient to explain the degree of carbon dioxide retention, or anoxia, from which she suffers. Similarly, there is no evidence of renal dysfunction to explain the findings. In addition, it has been shown that the metabolic abnormalities can be reversed by firmly ordering the patient to hyperventilate for a suitable period. When the blood gas concentrations have returned to normal values, the patient is alert, provides a more detailed medical history, and no longer complains of drowsiness. Her EEG also becomes normal and has higher frequencies, resembling the Harvard F-I type.

All these findings strongly suggest that there is a lesion within the central nervous system, similar in location to, but more chronic than, that described by Sarnoff,

Whittenberger, and Affeldt<sup>5</sup> in poliomyelitis. There is strong presumptive evidence by historical account that this patient suffered from an acute attack of acute epidemic encephalitis at the age of 17. At the present time she is unable to converge her eyes and has a static tremor. It is clear that the present findings do not enable us to make a definite diagnosis of acute epidemic encephalitis. However, they are evidence in favor of this presumption. During convalescence she was sleepy for a three-month period. One may wonder whether she did not suffer from carbon dioxide retention on a more transient basis at that time.

It is known that the major stimulus to respiration (depth and rate) is the level of arterial carbon dioxide in the region of the "respiratory center." Small increases in inspired carbon dioxide concentrations will immediately result in an increased respiratory minute volume if the lungs are capable of moving air through the respiratory passages. In this patient, who had no ventilatory abnormalities, increased inspired carbon dioxide produced no observable change in respiratory rate. Salicylates, which appear to increase the sensitivity of the respiratory centers to carbon dioxide, were also ineffective in increasing her respiratory rate or depth sufficiently to "blow off" the  $\text{CO}_2$ .

We are forced to conclude, therefore, that the respiratory center was unresponsive to carbon dioxide, at least to a concentration of 78 vol. % in her blood, and to assume that her respiration was "driven" by the low level of arterial oxygen saturation (via the aortic body reflex). This conclusion is substantiated by the results of prolonged hyperventilation. When the carbon dioxide had been lowered, and the oxygen tension increased, a period of marked bradypnea ensued, which resulted in a fall of oxygen saturation to 74% within three and one-half minutes. On the other hand, this patient, like those of Sarnoff et al., was still able to "drive" her respiratory mechanism



from higher voluntary centers, thus indicating that these pathways are intact as they course through the upper brain stem toward the medulla. There are no neurological data which enable us to localize this lesion more precisely. This voluntary control of respiration enabled her to maintain the same  $p\text{CO}_2$ , even during  $\text{O}_2$  breathing, because of the instruction given to breathe evenly and regularly.

It has been reported by Gibbs et al.<sup>11</sup> and by several other workers that increasing the carbon dioxide content of the inspired air will produce a modification in the cortical frequency spectrum toward faster frequencies. There has, however, been con-

siderable investigation of this problem, which cannot be reviewed in detail here. Meduna<sup>12</sup> and Morrice<sup>13</sup> have demonstrated that carbon dioxide in low concentrations (5%-10%) will produce an increase in the mean EEG frequency, but inhalation of high concentrations (30%) will regularly produce bilaterally synchronous delta-wave activity. Hill and Flack<sup>14</sup> also showed that in cats and dogs 10%-25% carbon dioxide produced vagal and vasomotor stimulation, whereas more than 25% resulted in narcosis. Indeed, Morrice's records of the EEG after 30% carbon dioxide inhalation are similar to those of our patient in the resting state.

#### HYPOTHETICAL CURVE

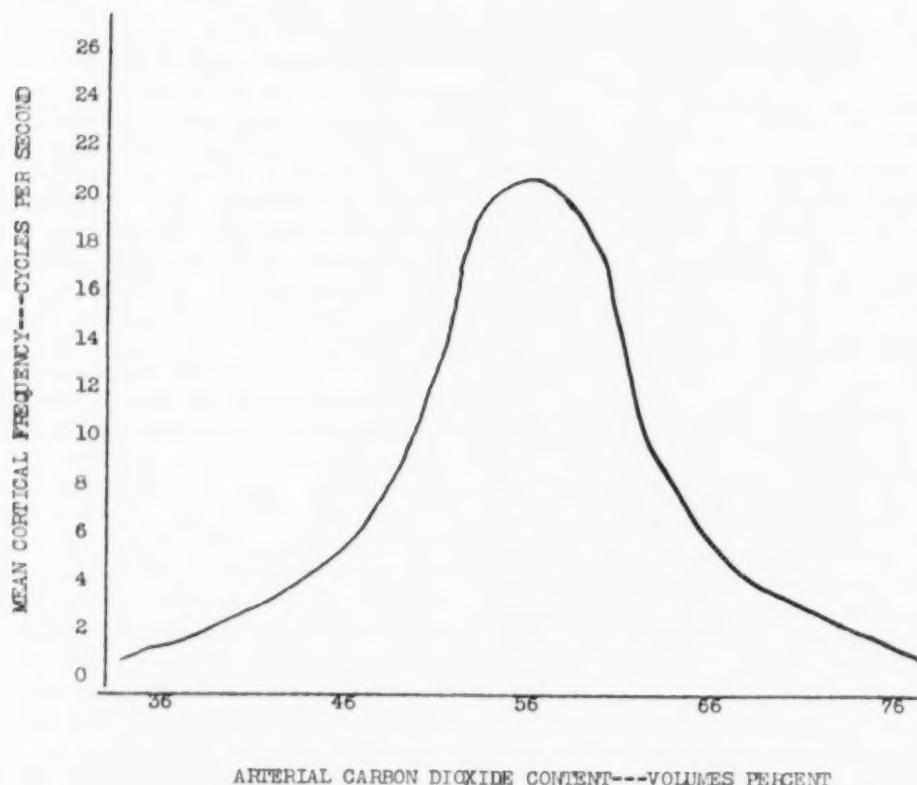


Fig. 8.—Hypothetical curve.

A number of workers have found that high concentrations of carbon dioxide stopped the convulsions of epileptics or inhibited seizures induced by insulin, picrotoxin, pentylenetetrazol (Metrazol), and electric shock.

Brazier<sup>15</sup> has observed that the EEG slows when carbon dioxide is retained during anesthesia.

The apparent divergence between the EEG effects of high and low carbon dioxide concentrations may perhaps be explained by postulating a bell-shaped curve (Fig. 8). On the rising slope of the curve a slight increase in CO<sub>2</sub> content will produce an increase in the mean frequency, but, once beyond the crest of the curve, further increases of arterial carbon dioxide levels will produce a slowing of the mean frequency.

The maximum carbon dioxide level producing an increased mean cortical frequency which was reported in Gibbs' paper was only 54.0 vol. % in the jugular vein. In our patient, the arterial carbon dioxide content (necessarily lower than the venous jugular carbon dioxide level) was never, even after nine and one-half minutes of hyperventilation, lower than 55.48 vol. %. This would represent a jugular carbon dioxide content of at least 60 vol. %. It is clear from this comparison that we are dealing with much higher levels of carbon dioxide content than Gibbs et al. and this may go far to explain why we observed the "anesthetic" or "narcotic" effect of carbon dioxide on the EEG. Inspection of the EEG after hyperventilation (Fig. 3) shows that this record is actually rather fast in its mean frequency (Harvard F-I type), and this may be due to the mildly elevated carbon dioxide content after hyperventilation. This EEG pattern is consistent with Gibbs' description of the "fast" EEG after 10% CO<sub>2</sub> inhalation. The normal subject may functionally operate on the left half of the curve, while the behavior of the patient in this case report is represented by

the right half of the curve, with a shift toward the left during hyperventilation.

### Summary

The case of a patient with chronic respiratory acidosis is presented.

An unusual electroencephalographic abnormality in the response to hyperventilation was discovered and was related to blood carbon dioxide content.

This metabolic abnormality is ascribed to an insensitivity of the respiratory center to carbon dioxide retention.

It was postulated that this insensitivity was most likely a sequel of epidemic encephalitis.

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# Cerebral Changes Revealed by Radioautography with $S^{35}$ -Labeled L-Methionine

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This radioautographic study was undertaken to ascertain the fate of radiosulfur in the brains of rats receiving  $S^{35}$ -labeled L-methionine under a variety of experimental conditions. As reported elsewhere,<sup>9,10</sup> it was of great interest to find in the initial experiments that under normal conditions the cerebral radioautograms showed depths of contrast that gave them a striking resemblance to Nissl-stained sections. While this work was in progress, Cohn et al. published an abstract summarizing cerebral radioautographic studies in which they used the same labeled amino acid.<sup>9</sup> By biochemical methods they found that the radioactivity was "mainly due to protein-bound  $S^{35}$ ." They observed that "the incorporation of  $S^{35}$  into the proteins was considerably greater in the regions containing cell bodies than in the white matter" and pointed out that "it was particularly prominent in the pyramidalis layer of Ammon's horn [hippocampus] and in the 'neurosecretory cells' of the supraoptic nucleus of the hypothalamus."

The present communication will deal with exploratory experiments in which a comparison was made between cerebral radioautograms of controls and those of animals subjected to a variety of experimental conditions. Results will be given of the respective effects of colloidal thorium dioxide (Thorotrast), whole-body x-irradiation,

insulin convulsions, infection, anesthesia, and reserpine on the incorporation of radiosulfur in the brain. A short description will also be given of attempts to use the isotope in the study of the formation of proteins in the spinal fluid.

## Experimental Procedure

Sixty-five male rats, weighing 250 to 300 gm., were used for these experiments. Thirty-five brains were prepared for radioautographic study.  $S^{35}$ -labeled L-methionine, with a specific activity of 25  $\mu$ c to 100  $\mu$ c per milligram, was administered intraperitoneally in amounts ranging from 1 to 4 mg. The time of administration varied according to the demands of the experiment. Except for the variable under investigation, all conditions pertaining to diet, environment, bodily handling, and treatment were the same for control and experimental animals, both before and throughout each experiment. At the end of an experiment, each animal was rapidly anesthetized with ether, and saline was perfused through the heart until the circulatory system was clear of blood. Thereafter the brain was fixed in situ by perfusion with 10% formalin and isotonic saline. The brains of a control and one or more experimental animals were so placed on the microtome that comparable transverse sections could be obtained at one cutting and mounted on a single slide. This ensured a radioautographic comparison of sections of equal thickness, as well as identical photographic processing. Although the serial frozen section technique has the advantage of avoiding shrinkage of tissue, it was difficult to cut simultaneously more than two brains by this method. Therefore, in most of these experiments the brains were embedded in paraffin, and this made it a simple matter to cut as many as five brains at the same time (Fig. 1). Sections were usually cut at 15  $\mu$  and exposed by contact to Kodak Medical X-Ray Film for periods generally not exceeding a week. The usual developing process was employed. Subsequently, the sections were stained either with thionine or with gallo-

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### General Considerations

Well-differentiated radioautograms were obtained from rats killed within the first hour following the intraperitoneal injection of radiomethionine. Paper electrophoretic studies revealed that at this time 94% to 97% of the radioactivity in the blood precipitated out with the proteins. Radioautograms from animals killed after longer intervals of time (up to 4 days) were comparable in intensity to those at the 24-hour period.

As reported elsewhere,<sup>9,10</sup> and as illustrated by the upper and lower right-hand sections of Figure 2, such radioautograms show depths of contrast that give them a striking resemblance to Nissl-stained sections. Accordingly, one finds the following parallels: (1) The radioactivity manifests itself predominantly in the gray matter; (2) the limbic cortex, generally, and the hippocampal formation, in particular, appear darker in the radioautogram than the neocortex; (3) the cerebellar cortex is also conspicuously dark; (4) in correspondence with their deep coloration in the Nissl stain, such subcortical structures as the supraoptic, paraventricular, ventromedial, and tuberal nuclei of the hypothalamus; the anterodorsal and medial habenular nuclei of the thalamus; the interpenduncular nucleus of the midbrain; the pontine nuclei, etc., appear much darker in the film than other nuclear formations. The pituitary and pineal glands, as well as the choroid plexus and ependymal lining, appear black in the film.

### Thorotrast and Whole-Body X-Irradiation

The following experiments were suggested by the demonstration in this laboratory that whole-body x-irradiation or the systemic administration of Thorotrast results in an alteration of an animal's protein metabolism.<sup>6</sup> One group of animals received an intravenous injection of Thorotrast in a dose of 0.5 cc. per 100 gm. of body weight on the day before the admin-

istration of radiomethionine. A second group was subjected to 300 r of whole-body x-radiation 36 hours prior to injecting the isotope. Another group was used for control. All animals were killed six hours after receiving the radiomethionine.

*Thorotrast.*—As compared with the controls, the rats receiving Thorotrast showed some generalized increase in radioactivity in the cellular parts of the brain. The picture was otherwise the same as in the controls. These results appeared to be correlated with Gabrieli and Chang's findings of nearly a 70% increase in the serum protein radioactivity in animals previously treated with Thorotrast.<sup>6</sup>

*X-radiation.*—In the case of animals receiving whole-body radiation, there was no detectable alteration in the intensity of the radioautogram. This was in keeping with the absence of any appreciable change in the serum proteins at the particular time these animals were killed.<sup>6</sup>

### Infection

In the course of this study, it was noted that radioautograms from animals suffering from an intercurrent infection, such as a pulmonary abscess, were barely fogged, as compared with the controls, a finding that suggested a generalized depression in the incorporation of S<sup>35</sup>. There was a correspondingly low radioactivity of the serum proteins. An experiment was performed which indicated that these observations were not chance findings. To induce infection, we used a strain of *Escherichia coli* communis which was of known virulence when injected intravenously into a rat that had previously been subjected to a unilateral ureteral ligation.\* Animals prepared in this manner were administered radiomethionine intraperitoneally as soon as lethargy and diarrhea were manifest and were then killed one hour later. As compared with the controls, the radioautograms of these animals showed a generalized reduction in radioactivity.

\* Dr. Paul Beeson suggested this procedure and provided the strain of organisms.

### Convulsions

In line with what has frequently been described in previous studies, Lorentzen has recently provided further evidence to support the contention that a Nissl type of stain reveals a loss of nucleoprotein from nerve cells of animals subjected to insulin convulsions.<sup>8</sup> In the present study, radioautograms were obtained from insulin-convulsed animals that brought into striking contrast parts of the brain that appeared chromophobic, or questionably chromophobic, in Nissl-stained sections.

Rats fasted for 24 hours and kept at an environmental temperature of 26 C were treated on the average with 6 units of unmodified insulin. As illustrated in the radioautogram labeled *B* in Figure 1, when radiomethionine was given simultaneously with insulin and the animal killed after its first convulsion, there was only slight generalized decrease in the intensity of the radioautogram as compared with the control (middle of Figure). The bottom two radioautograms show, however, that when the isotope was injected after the onset of convulsions, there was evidence of a marked decrease in radioactivity throughout the brain. Further details of this experiment are given in the legend of the Figure.

The radioautograms in Figure 2*A* are from another experiment and show sections through the left and right hemispheres, respectively, of an experimental and a control animal. Curiously enough, in this instance the pyriform cortex of the experimental animal (left side of Figure), as well as a number of subcortical structures, such as the perithalamic reticulum, did not show the same degree of change as other parts of the brain. It should be emphasized that the hippocampal cortex, which ordinarily reveals a very high degree of radioactivity, appears in the film as pale as the neocortex. As illustrated in Figure 2*B*, Nissl-stained sections suggested corresponding, but much less striking, differences.

Fig. 1.—Radioautograms of rat brain sections from two control and three experimental animals, each receiving intraperitoneal injection of 110 $\mu$ c S<sup>35</sup>-labeled L-methionine. Experimental animals were convulsed with 6 units of insulin injection U.S.P. (unmodified insulin). Sections were cut simultaneously and mounted together to ensure equal thickness and identical processing. *A* and *C*, from control animals killed one and two and one-half hours, respectively, after injection of radiomethionine. *B*, from animal given insulin simultaneously with radiomethionine and killed after first convulsion, two and one-half hours later. *D* and *E*, from animals receiving insulin, followed by radiomethionine 15 minutes subsequent to initial seizure; both animals killed 1 hour later. In case of *D*, the animal received 500 mg. of dextrose in 10% solution with the radiomethionine and ceased to convulse. In case of *E*, no dextrose was given and the animal remained in coma.

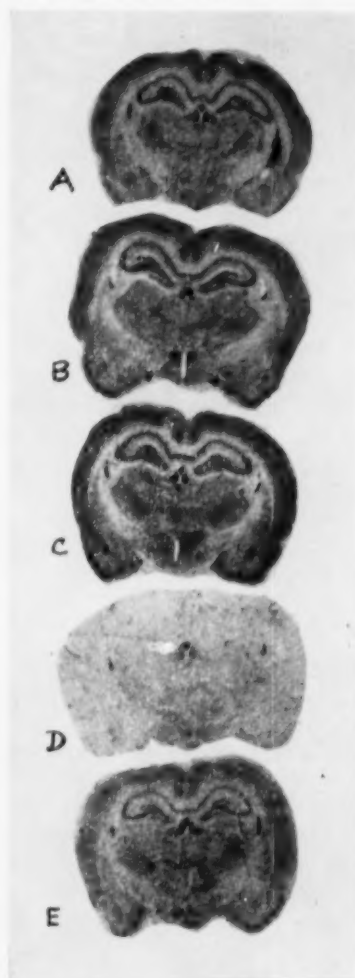
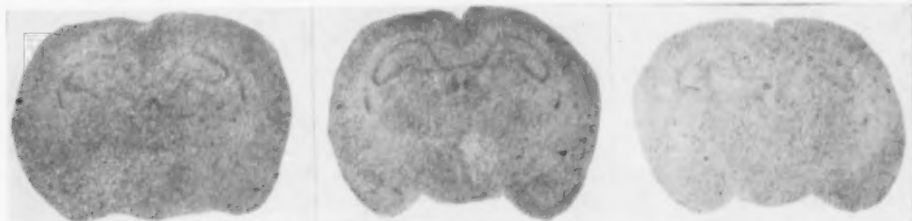




Fig. 2.—A, radioautographs of comparable sections from hemispheres of a control (right) and a convulsed animal (left). Sections cut simultaneously and mounted together to ensure that they would be of equal thickness and subject to identical photographic processing. The experimental animal had insulin-induced convulsions for an hour prior to the administration of  $S^{35}$ -labeled L-methionine. Its brain shows considerably less radioactivity than the control's. In contrast to the control, note that the region of the hippocampus is as pale as the neocortex. Curiously enough, in this instance the pyriform cortex and perithalamic reticulum were not affected to the same degree as other parts of the brain.

B, Nissl-stained sections from same experiment suggested corresponding, but much less striking, differences.

Fig. 3.—Radioautographs of comparable brain sections from a control and two reserpine-treated rats. Sections cut simultaneously and mounted together to ensure that they would be of equal thickness and subject to identical photographic processing. The rat whose radioautograph is shown at right received reserpine three and one days prior to administration of  $S^{35}$ -labeled L-methionine. The other treated animal (left side of Figure) received a single dose on the day before. Section from control is shown in middle of Figure. See text for further description.



### Neuropharmacological Agents

The following two experiments are illustrative of the usefulness of radioautographic methods in studying the effects of neuropharmacological agents on the brain's metabolism.

**Reserpine.**—Reserpine is now widely used for the treatment of psychiatric disorders and hypertensive cardiovascular disease. The mechanism of action of this drug remains obscure. In the following experiment, reserpine (Serpasil) was injected intraperitoneally in rats one and three days prior to the administration of radiomethionine. It was given in a dose of 1 mg/kg. The animals were killed one hour following the intraperitoneal injection of  $75\mu\text{C}$  of the isotope. After the second injection of reserpine, the animal developed diarrhea, tended to remain motionless with its eyes closed, and manifested poor righting reflexes. As illustrated in the right-hand radioautogram of Figure 3, the brain from such an animal showed a marked generalized decrease in radioactivity as compared with the control's brain (middle of Figure). A single injection of reserpine resulted in similar, but less conspicuous, changes (left-hand radioautogram).

**Anesthesia.**—In this experiment, a commonly used laboratory anesthetic, diallylbarbituric acid U. S. P. (Dial) and urethan U. S. P. in combination, was administered to a group of rats. For reasons that will be explained subsequently, both the experimental and the control animals were placed



in a cold room at 9 C during the study. After 90 minutes of anesthesia, 100 $\mu$ c of radiomethionine was injected intraperitoneally in the experimental group, and the same dose was given to the controls. The animals were killed 45 minutes later. A dose of 0.04 gm. of diallylbarbituric acid and 0.16 gm. of urethan per kilogram, given subcutaneously, resulted in only a slight generalized decrease in radioactivity, as compared with the control. With twice this dose, however, there was a conspicuous generalized reduction in radioactivity.

In the foregoing experiments it is not justifiable to assume that the cerebral changes associated with reserpine and anesthesia were attributable to the direct action of the agents used on the nerve cells of the brain. In both instances there is the possibility that the changes were indirectly the result of disturbances of homeostatic mechanisms. The capacity of reserpine and anesthesia to produce hypothermia through interference with thermoregulatory mechanisms is one of the many factors that could contribute to such disturbances. Exposure to cold has been reported to result in changes of nucleic acid and protein formation in the brain.<sup>12</sup> The short-term nature of the experiments employing diallylbarbituric acid made it feasible to try to control the variable of temperature. As a first attempt in this regard, the condition of cold was superimposed on both the experimental and the control animals. The foregoing results may be considered conclusive only in so far as they showed that anesthesia in addition to exposure to cold gave a different radioautographic picture from that following cold alone.

#### Studies on Cerebrospinal Fluid

Upon undertaking this study, we hoped that information would be obtained as to whether the blood-brain barrier plays a role in the formation of proteins appearing in the cerebrospinal fluid. Paper electrophoresis was used to study the radioactivity of the various protein fractions of the serum and the cerebrospinal fluid. The radio-

activity pattern of the serum proteins could be matched quite readily with the colorimetric electrophoretic pattern.<sup>6</sup> Unfortunately, however, it proved to be impossible to obtain enough spinal fluid from the rat to permit concentration in the usual manner for colorimetric electrophoretic studies. In the unconcentrated fluid there was insufficient radioactivity to give more than a suggestion of the peaks of the protein fractions. This was true even after eight hours was allowed for the assimilation of as much as four times the amount of labeled methionine necessary to obtain a satisfactory pattern of the serum proteins.

#### Comment

The present investigation was designed to explore the possibility of whether or not the administration of radiomethionine would allow one to detect differential changes in the incorporation of radioactivity in the brain under a variety of experimental conditions. The finding that such changes can be demonstrated has many implications, but the following discussion will confine itself to those that stem immediately from the work that has been reported.

Existing knowledge of the role of methionine in general metabolism, together with the cerebral radioautographic and biochemical studies of Cohn et al.,<sup>3</sup> leads one to assume that when radiomethionine is injected into an animal it is utilized in the metabolism of proteins in the brain. If this assumption proves to be correct, methods of the kind used in the present study will provide a simple means of screening the entire brain for the purpose of obtaining a qualitative appraisal of the effect of various experimental conditions on the anabolic phase of the cerebral metabolism of proteins. After such screening, the application of a number of refinements in radioautographic techniques would afford a means of obtaining some quantification of detected changes.

The qualitative nature of the method employed in the present study makes one reluctant to read into the radioautograms



more than the generalized changes that have been described. Except in the insulin experiments, in which they were so obvious in one instance, no mention was made of differential changes in specific neural structures. But this is a matter that deserves further elaboration. In the experiments involving reserpine, anesthesia, and infection, one obtained the impression that structures usually showing a high degree of activity were relatively more affected than those that normally showed only little or moderate activity. It is conceivable, therefore, that structures characterized by high radioactivity might suffer more than others from metabolic disturbances of the kind reflected in these experiments.

The bearing of such a possibility on electroencephalographic and behavioral changes seen in reserpine-treated cats has been considered elsewhere in a paper dealing with the hippocampus and its functional role as part of the limbic system.<sup>10</sup> As noted above, the limbic cortex, generally, and its hippocampal portion, in particular, show a higher degree of radioactivity than the neocortex. The limbic cortex, i. e., the cortex of the great limbic lobe, comprises most of the phylogenetically old cortex. If it should subsequently be shown that the aforementioned radioautographic contrasts can be attributed to quantitative differences of radioactivity in the elements of the structures under consideration, the finding will have significant implications in regard to the alleged dichotomy in function of the "old" and the "new" cortex.<sup>10</sup> In those parts of the limbic cortex that have thus far been examined, there has been found high cholinacetylase<sup>5</sup> and cholinesterase<sup>1</sup> activity. The question therefore arises as to whether or not the high radioactivity seen in the limbic cortex and a number of other cerebral structures reflects a preferential utilization of methionine in protein anabolism, possibly correlated with acetylcholine systems and/or high cellular activity.

The radioautographic picture seen in cases of infection is suggestive that a depression

in the anabolic phase of metabolism may be a contributing factor in the symptomatology related to the nervous system during infectious, febrile illnesses, e. g., lassitude, apathy, delirium, etc. In the light of this possibility, it would appear to be a matter of great practical importance to employ radioautographic methods to test the therapeutic hypothesis that the provision of an abundant supply of readily assimilated nutriment is conducive to restoring the anabolic phase of protein metabolism.

The results of the studies on infection and convulsions, when considered together, raise questions that bear on the predisposition of some children to seizures during febrile illnesses. Do untoward changes in protein metabolism during the illness make the patient more susceptible to seizures? Do the seizures, in turn, aggravate an already deleterious process?

As long ago as the 19th century, it was inferred on the basis of Nissl studies that increased functional activity or morbid processes may lead to marked alterations in the content of nucleoproteins in nerve cells.<sup>11</sup> The semiquantitative spectromicroscopic studies of Caspersson,<sup>2</sup> Hydén,<sup>7</sup> and others not only have provided more conclusive evidence that such an inference is correct but also have indicated in a more convincing manner that large fluctuations in the formation or depletion of nucleoproteins may occur at a rapid rate. The present studies have yielded information that may prove to shed further light on the foregoing problem. In the first place, they have shown that following the administration of radiomethionine the degree of intensity of radioactivity in cerebral radioautograms parallels the intensity of staining seen in Nissl preparations. In the second place, in some experiments radioautograms were obtained that brought into striking contrast parts of the brain that appeared chromophobic, or questionably chromophobic, in Nissl-stained sections. These findings indicate the potential usefulness of radioautographic methods for demon-

strating dynamic alterations in the metabolism of the brain.

### Summary

A radioautographic study was undertaken to ascertain the fate of radiosulfur in the brains of rats receiving  $S^{35}$ -labeled L-methionine under a variety of experimental conditions. Exploratory experiments are reported in which a comparison was made between the cerebral radioautograms of controls and those of animals that were, respectively, given colloidal thorium dioxide (Thorotrast), whole-body x-irradiation, infection, insulin convulsions, diallylbarbituric acid (Dial), and reserpine.

Under normal conditions the cerebral radioautograms showed depths of contrast that gave them a striking resemblance to Nissl-stained sections. The degree of intensity of radioactivity paralleled the intensity of staining seen in Nissl preparations. Following whole-body x-irradiation (300 r) there was no detectable change between the brains of control and those of experimental animals. Thorotrast resulted in a slight generalized increase in radioactivity. With infection, reserpine, and diallylbarbituric acid anesthesia, there was a generalized decrease. This change was suggestively greater in structures normally showing high radioactivity. Following insulin-induced convulsions there was also a generalized decrease in radioactivity, and in one instance differential changes were clearly discernible in the hippocampus. In these latter experiments, radioautograms brought into striking contrast parts of the brain that appeared chromophobic, or questionably chromophobic, in Nissl-stained sections.

Some of the implications of the foregoing work are considered in the discussion.

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# Histopathology of Psychomotor Epilepsy

## *A Study with Silver Carbonate*

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In the first decade of this century Alzheimer<sup>1</sup> published his fundamental studies of the histopathology of epilepsy. He described in detail degeneration of the glia characterized by swelling of the cytoplasm of the cells and fragmentation of their processes and designated this type of destruction as "ameboid glia." Alzheimer stated that ameboid disintegration (elasmatodendrosis) was a sign of grave damage to the nerve tissue, that it was commoner in the white matter, and that degeneration of the neurons was less impressive. There was no

further progress after the days of Alzheimer because the usefulness of the older technical methods was exhausted.

In recent years new developments permitted a more detailed analysis of this disorder: introduction of electroencephalography, development of surgical therapy, making human biopsy material available, and selective histologic analysis with the silver carbonate methods of del Rio Hortega.

### Present Study

**Material.**—This investigation is based on human biopsy material from the temporal lobes of 60 cases of psychomotor epilepsy: Of these, 45 cases were placed at my disposal by Dr. Percival Bailey, of Chicago, and 15 cases were treated in the University of Michigan Hospital or were obtained from other sources; 9 cases were utilized for illustrations; 7 of these were from Dr. Bailey.

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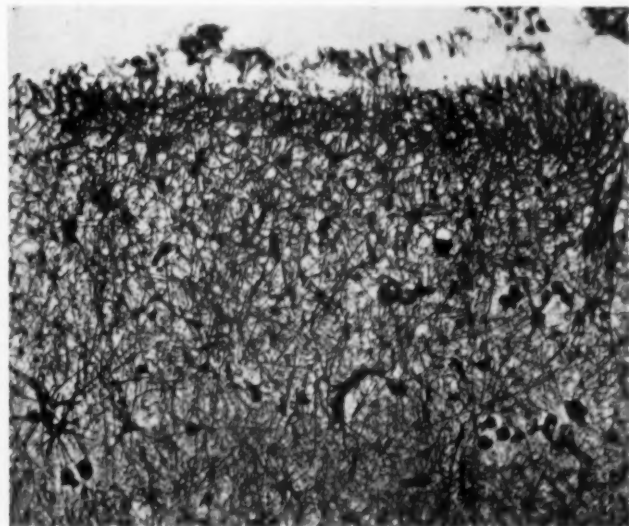


Fig. 1.—Dense astroglia of the first, second, and upper part of the third layer;  $\times 100$ .

Fig. 2.—Intense proliferation of astroglia in the lower layers of the cortex; reduced to 88% of mag.  $\times 200$ .

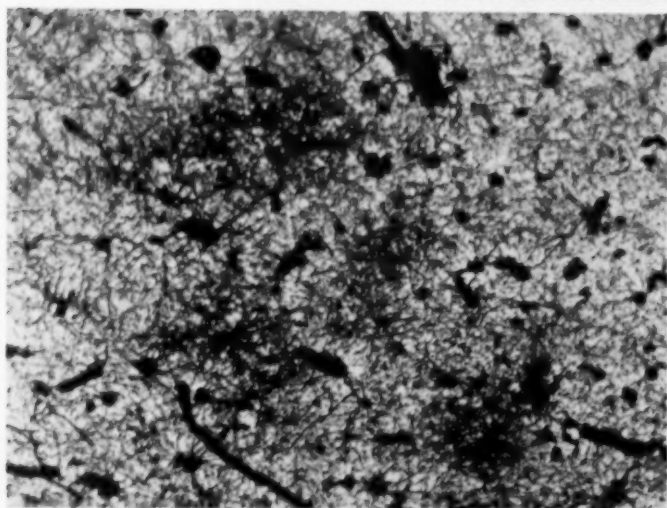
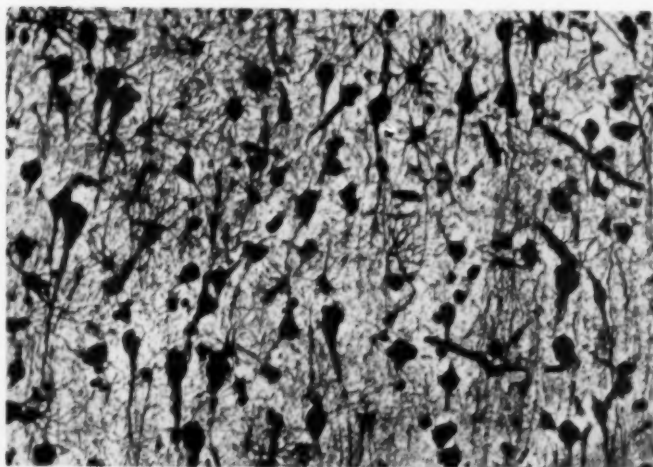


Fig. 3.—Focal scars in the subpial zone; reduced to 88% of mag.  $\times 100$ .

Fig. 4.—Shrunk neuron surrounded by processes of a giant astrocyte in preameboid state; reduced to 76% of mag.  $\times 400$ .

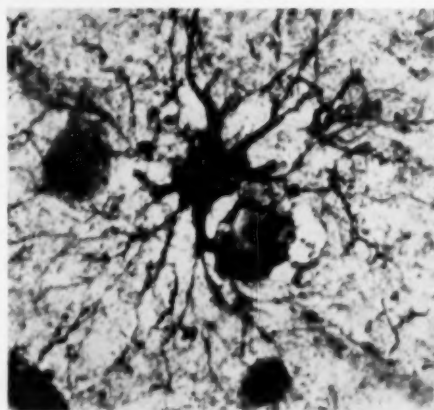
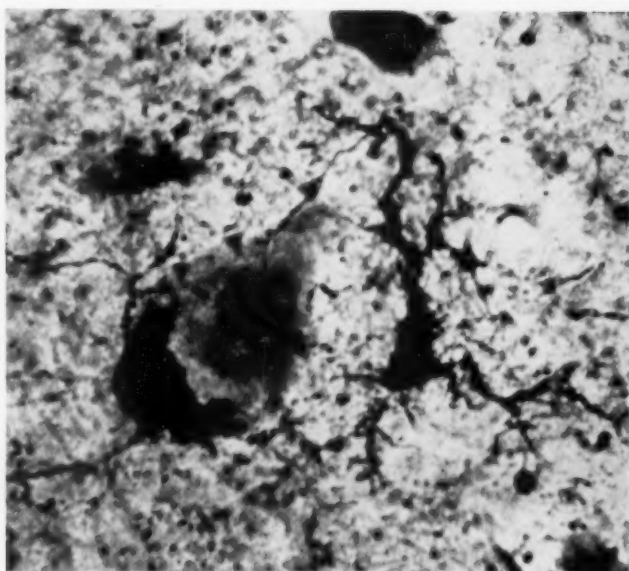


Fig. 5.—Swollen and degenerated neuron surrounded by hypertrophic microglia and oligodendroglia in preameboid state;  $\times 400$ .



The biopsy specimens measured from 1.5 $\times$ 2 to 2 $\times$ 3 cm. The tissue appeared normal to the unaided eye and was free from traumatic lesions, atrophy, or neoplasm. The tissue was cut on the freezing microtome at 15 $\mu$  and was treated with numerous variants of the silver carbonate technique.

*Findings.*—With these procedures it was possible to analyze various histopathologic phenomena, many of which were not previously known. In general, the histopathologic changes could be divided into two groups:

(1) proliferation, hypertrophy, and degeneration of the glia, and (2) degeneration and necrosis of the neurons and of their satellites.

*Cortex:* Proliferation and hypertrophy of the glia were very distinct in the first layer; there was always a dense network of astroglia, in which two distinctly different zones could be distinguished: a compact subpial layer (Fig. 1) and a less dense network of astrocytes beneath it that spread into all

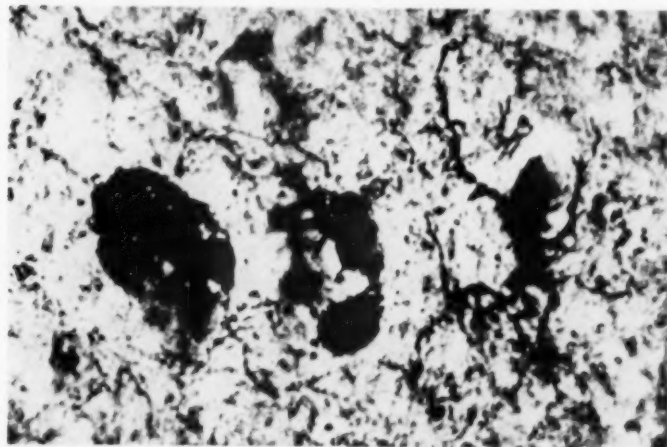


Fig. 6. — Destroyed neurons covered by a network of hypertrophic oligodendroglia; reduced to 88% of mag.  $\times 400$ .

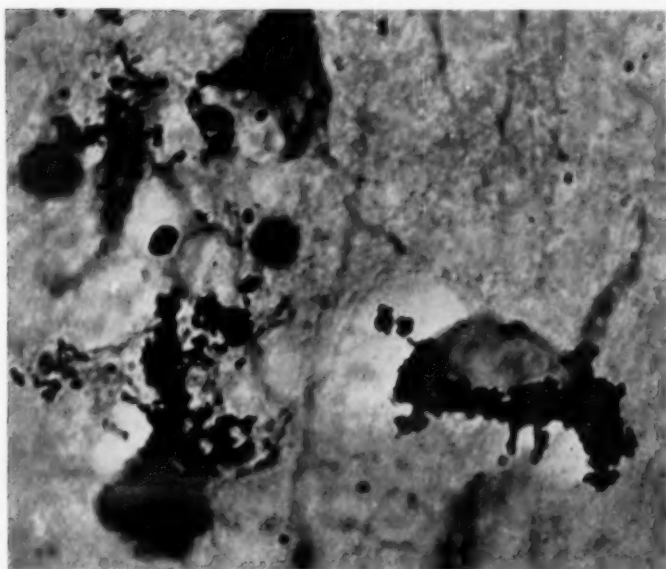


Fig. 7.—Degenerated and swollen neurons partly surrounded by degenerated satellites;  $\times 400$ .

layers of the cortex (Fig. 2). In the subpial zone there were frequently numerous well-defined amorphous scars (Fig. 3).

Necrotic phenomena were common in the gray matter, and there could be distinguished four types: (*a*) necrosis of the neurons and their auxiliary systems; (*b*) focal necrosis, which was restricted to smaller areas or involved the entire width of the cortex; (*c*) diffuse necrosis, and (*d*) laminar necrosis.

Fig. 8.—Group of necrotic neurons and their satellites; reduced to 70% of mag.  $\times 400$ .

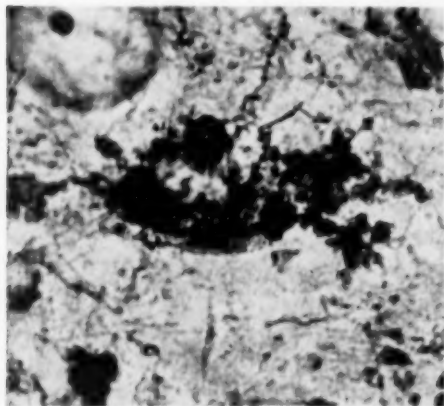
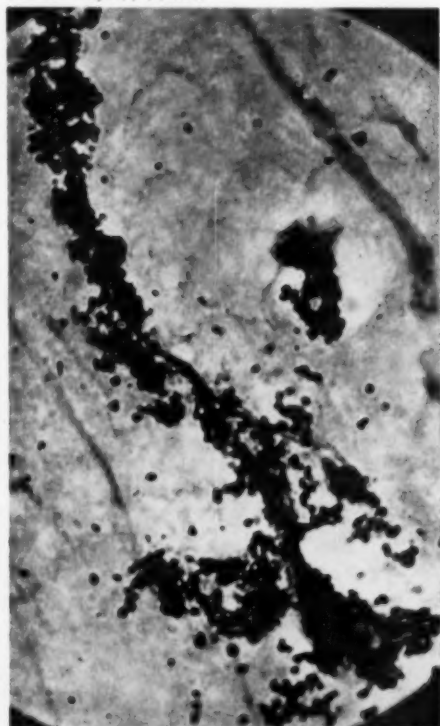


Fig. 9.—Neuron with distinctly visible body and neurite surrounded by necrotic perisomatic and periaxonic glia (state of necrotic preservation of Cajal);  $\times 400$ .





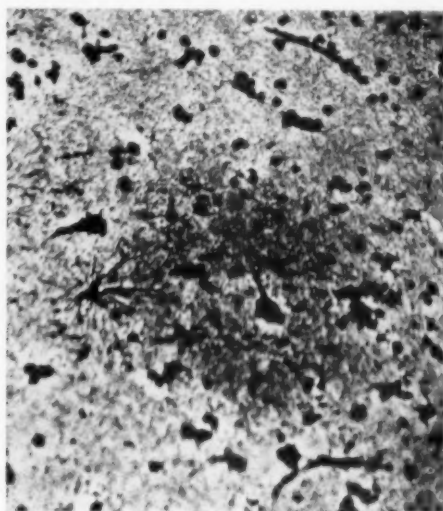


Fig. 10.—Small necrotic focus with a shrunken neuron in its center; reduced to 84% of mag.  $\times 100$ .

A. Necrosis of neurons and their satellites, which was present in all cases, with numerous transitional types.

1. The neuron was shrunken and its processes were destroyed; the cytoplasm and the nucleus stained dark, and their structures were poorly outlined. The destroyed nerve cell was surrounded by processes of a giant

astrocyte in the preameboid state of disintegration (Fig. 4).

2. A swollen neuron with an enlarged and partly destroyed nucleus was surrounded by hypertrophic and swollen microglia and oligodendroglia cells (Fig. 5).

3. Frequently remnants of disintegrated nerve cells were covered by a network of hypertrophic oligodendrocytes (Fig. 6).

4. Swollen neurons, without a trace of normal structure, were partly surrounded by necrotic satellites (Fig. 7).

5. Very impressive were small groups of destroyed neurons surrounded by masses of necrotic auxiliary cells (Fig. 8).

6. A necrotic parenchyma cell with body and neurite distinctly visible was surrounded by necrotic perisomatic and periaxonic glia (state of necrotic preservation of Cajal) (Fig. 9).

#### B. Focal Necrosis.

1. Small foci of necrosis with a shrunken neuron in its center, surrounded by a belt of necrotic tissue (Fig. 10).

2. Large areas of necrosis which involved all layers of the cortex but remained relatively well demarcated (Fig. 11).

C. Diffuse necrosis of all layers of the cortex with fragmentation of all structures

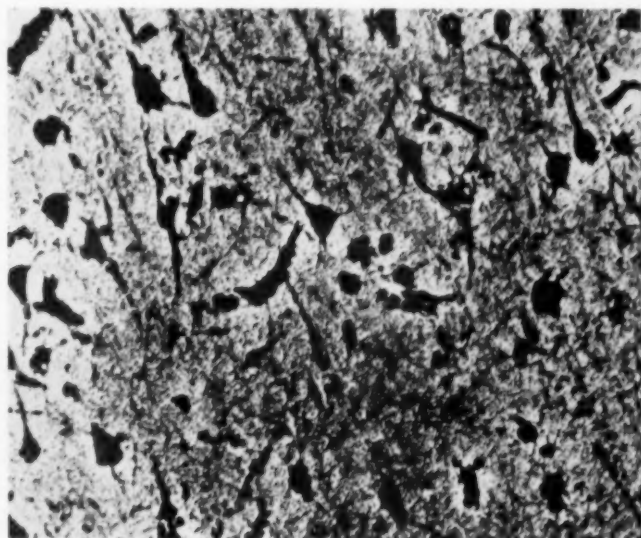


Fig. 11. — Relatively well - demarcated necrotic area which involves all layers of the cortex;  $\times 100$ .



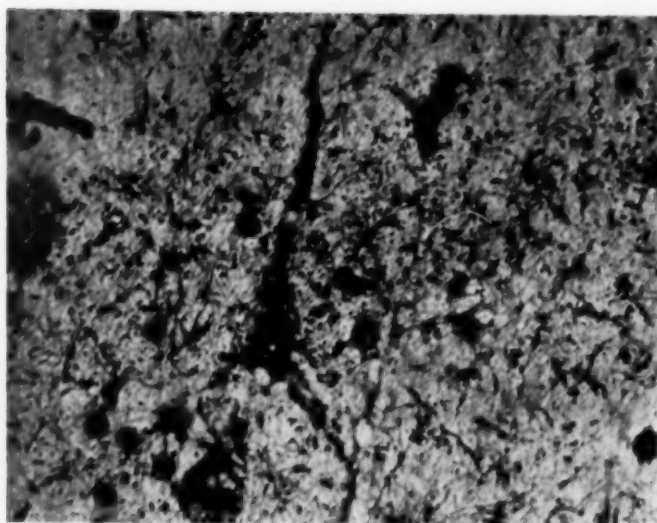
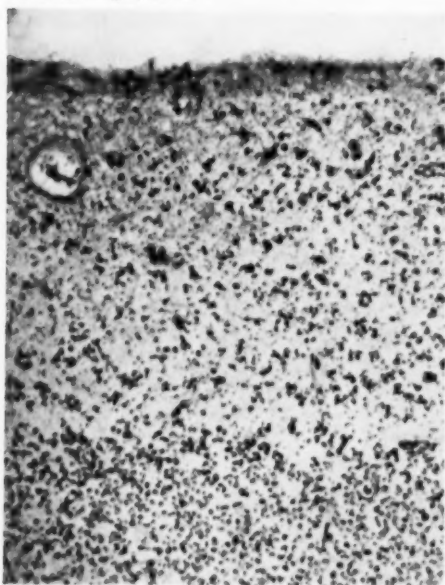


Fig. 12.—Diffuse necrotic area with advanced disturbance of the architecture;  $\times 400$ .

and severe disturbance of the architecture (Fig. 12).

D. Necrosis of all layers with preservation of the laminar character of the cortex (Fig. 13).

Fig. 13.—Necrosis of neurons and their satellites in all layers with preservation of the laminar character of the cortex; reduced to 80% of mag.  $\times 100$ .



Vessels: The perivascular glia cells of all types in the cortex and in the white matter were affected in a manner similar to that of the auxiliary elements of the neurons. The microglia was hypertrophic and was frequently in process of migration (Fig. 14); all perivascular elements were gradually disintegrated, and in the final stage the vessels were surrounded by necrotic glia (Fig. 15). The pericytes were affected in

Fig. 14.—Hypertrophic perivascular microglia in state of migration; reduced to 84% of mag.  $\times 400$ .

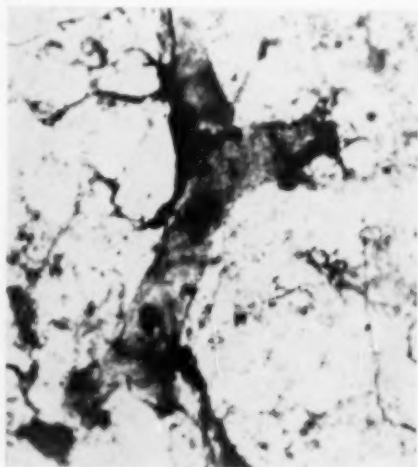
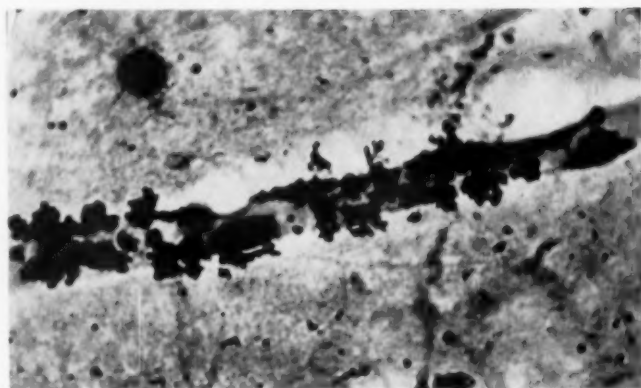


Fig. 15.—Final stage of destruction of the perivascular glia: The vessel is surrounded by shrunken necrotic cells. Reduced to 92% of mag.  $\times 400$ .



similar manner: Their cytoplasm was hypertrophic, and an intricate network of their processes was partly necrotic; the endothelial cells were greatly swollen (Fig. 16).

In the white matter the histologic picture was characterized by proliferation of astroglia, with numerous "monster astrocytes" of Weigert, swelling of the oligodendroglia (Fig. 17), ameboid degeneration of Alzheimer (Fig. 18), and numerous areas of diffuse (Fig. 19) and focal necrosis.

#### Comment

The histopathologic findings here described leave no doubt that the dominant

change in psychomotor epilepsy is the destruction of the neurons and their auxiliary systems, that is, of the entire functioning unit of the parenchymatous cells. The significance of the satellite systems of the glia was demonstrated by del Rio Hortega,<sup>2</sup> who showed that the neuron is supported by an elaborate system of glia which has a definite structure. Del Rio Hortega distinguished in these systems two closely linked but morphologically different component parts: (1) the perisomatic glia, which surrounds the body of the neuron with a network of interconnected cells, and (2) the periaxonic glia, which supports the pro-

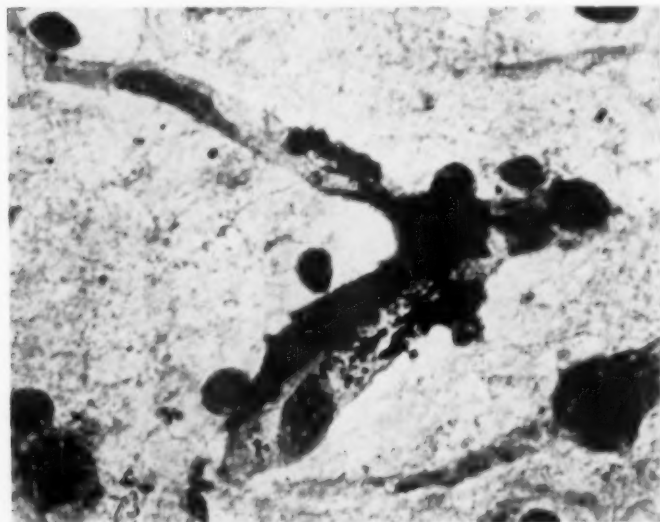


Fig. 16.—Partly destroyed pericyte in the gray matter;  $\times 400$ .

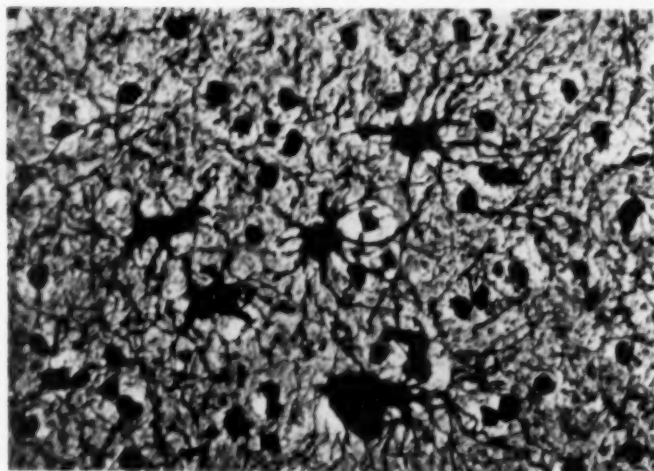


Fig. 17. — Hypertrophic astroglia and swollen oligodendroglia in the white matter; reduced to 90% of mag.  $\times 400$ .

cesses. These findings were confirmed by de Castro,<sup>3</sup> who described in the medulla of the cat perisomatic astroglia and periaxonic oligodendroglia, and by Scharenberg,<sup>4</sup> who studied the auxiliary glia in the human Gasserian ganglion. In the hypothalamus of man, Leopold Liss,<sup>5</sup> of this laboratory, demonstrated in silver carbonate preparations perisomatic and periaxonic astroglia (Fig. 20). The pathologic counterpart of this finding is demonstrated by Figure 9. These two illustrations (Figs. 9 and 20) show that the nerve cell and its satellites

are morphologically and physiologically closely linked and constitute a single physiologic entity, and that the supporting systems are vital for normal functioning of the neuron. In psychomotor epilepsy this physiologic entity is primarily attacked and the nerve cells and their satellites are destroyed. The damage to the nerve cells is reflected in degeneration of the neurons and by hypertrophy, proliferation, and degeneration of their satellites. The histologic findings strongly suggest that the neuron was struck first, since numerous necrotic nerve

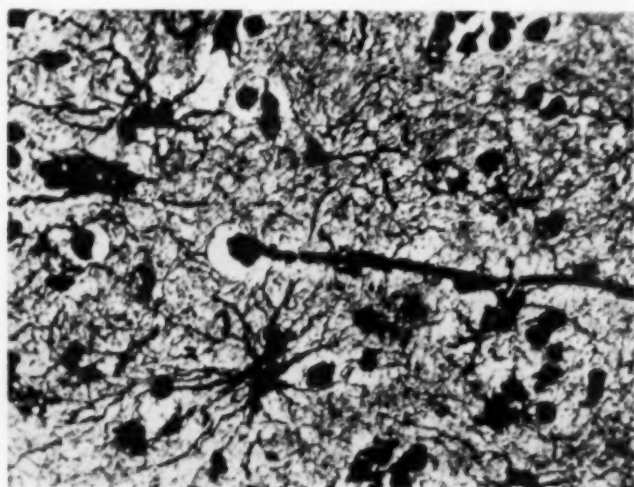


Fig. 18.—Preameboid and ameboid degeneration of the astroglia in the white matter; reduced to 92% of mag.  $\times 400$ .

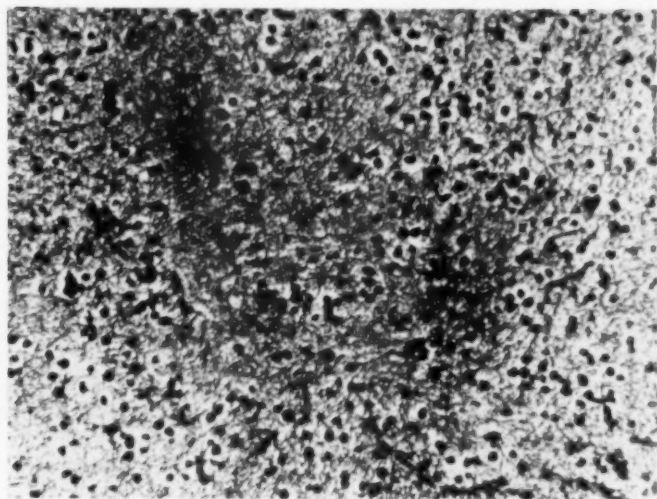


Fig. 19.—Focal necrosis of astroglia and oligodendroglia in the white matter; reduced to 88% of mag.  $\times 200$ .

Fig. 20.—Normal perisomatic and periaxonic astroglia in human hypothalamus (Dr. Leopold Liss);  $\times 400$ .



cells were surrounded by hypertrophic and active glia, and that the degeneration of the satellites occurred at a later stage. The vascular system was affected in a similar manner; the perivascular glia and the pericytes were hypertrophic and were gradually disintegrated; the endothelial cells were swollen.

In the white matter the dominant histopathologic change was ameboid degeneration of Alzheimer, which affected all types of glia and numerous foci of necrosis, similar in character to those in the cortex.

It is reasonable to conclude that the histopathologic changes of the neurons and their satellite cells here described are peculiar to psychomotor epilepsy, since these are not known to occur in other primary disorders of the parenchyma (Alzheimer's and Pick's disease; amaurotic idiocy) or in conditions in which ameboid degeneration of the glia is a dominant factor, such as acute and chronic catatonic states, toxic conditions (uremia), and many others.

All histopathologic changes here described were intravital, since they were present in carefully preserved biopsy material from patients who survived surgery, and many

of whom improved; in spite of the severity of these changes, they are compatible with life for years. The question arises whether these changes take place in other parts of the brain. Although autopsy material from patients examined was not available, there is reason to believe that in psychomotor epilepsy the whole central nervous system is affected; In one case both temporal lobes were examined, and the findings were identical; in three patients who were not treated surgically and died following status epilepticus ameboid disintegration was present throughout the brain, as previously described by Alzheimer. The degeneration of the parenchyma is not the result of grand mal attacks but may be the cause of the latter, as was demonstrated by another case: A 19-year-old youth was described as "epileptic since infancy"; he had numerous grand mal attacks and "epileptic psychosis." Diphenylhydantoin (Dilantin) relieved the convulsive attacks for 13 months but not the psychotic manifestations. The patient died of tuberculosis of the lungs, and histologic examination showed proliferation and hypertrophy of the glia and foci of preameboid and ameboid degeneration throughout the brain.

### Summary

In 60 cases of psychomotor epilepsy the silver carbonate method revealed extensive

destruction of the gray and the white matter of the temporal lobes. In the gray matter the neurons and their auxiliary systems of glia were affected, and there were numerous areas of necrosis. In the white matter ameboid degeneration of glia was the dominant change.

University of Michigan.

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# Pain-Spot Densities in Human Skin

## *An Experimental Study*

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It is common experience that pain sensitivity in the skin is not a uniform function. Exploration of a small area of the skin with a fine needle will reveal both highly sensitive spots and areas where pain is scarcely or not at all perceived. This variability has been repeatedly commented upon in major studies of cutaneous sensation.<sup>1-7</sup> A matter of some practical significance to the clinician, it has not been systematically examined in a quantitative way, particularly with reference to differences among individuals. Such an investigation is here reported.

### Method

A calibrated needle algometer with a 25-gauge piano-wire spring was used for obtaining pain thresholds (Fig. 1). A 24-gauge hypodermic needle with the hub removed was fastened to the piston in the barrel. The sharpness of the point was checked periodically under the microscope by a comparison with a standard. For the purposes of this study the algometer scale was divided into six equally spaced units.

Repeated calibrations over the period of study demonstrated no change in spring tension. This is illustrated graphically in Figure 2, in which the scale readings are plotted against grams of pressure acting on the algometer spring. Although several checks were made, only two curves, recorded nine months apart,

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Read by title at the 81st Annual Meeting of the American Neurological Association, Atlantic City, June 18-20, 1956.

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Fig. 1.—Test pattern on the dorsum of the hand and the needle algometer.

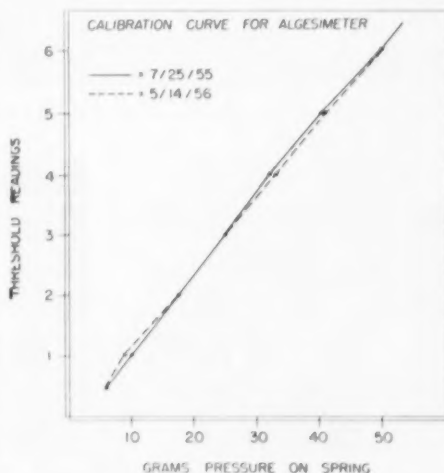


Fig. 2.—Calibration curve for algometer, demonstrating its relative constancy over a nine-month period.



are shown, indicating that over the period of use the spring tension remained constant.

A 2X2 cm. rubber stamp containing 49 evenly spaced squares was used to impress an inked pattern on the area to be tested. An additional spot was tested near the center in order to simplify the calculation of responses in percentages. A stamped area is shown on the dorsum of the hand in Figure 1.

The needle was inserted into the center of each square and the squares were tested in linear order, for preliminary studies showed no differences in results obtained by this method as compared with an order of testing in which the successive points stimulated were in widely separated rows. A record was made for each spot of the least pressure required to evoke the sensation of pain, as distinct from a feeling of touch, pressure, and sharpness. Since the highest reading on the algometer scale was 6, a response of pain elicited with pressure exceeding this value was arbitrarily represented by the number 7. A spot of skin withstanding the full weight of the algometer for five seconds after it had been lowered was defined as

"analgesic" and was represented by the letter *A*. The rate of descent of the algometer was found to modify the responses; lowering the instrument at about one-third the usual speed produced significantly lower pain thresholds. The rate, therefore, was kept as slow and as constant as possible.

One hundred fifty tests were made on 15 men and 6 women, all young adults in good health. The principal area studied was the dorsum of the hand. In six subjects the forehead, the shin, and the dorsum of the foot were also tested.

The effects on pain thresholds of erythema and of neural ischemia were observed in five subjects. First-degree burns were produced by ultraviolet irradiation, and ischemia was produced by inflation of a pneumatic cuff about the upper arm to greater-than-systolic pressure (150-170 mm. Hg).

### Results

There existed in every subject a wide range of pain sensitivity which was apparently unrelated to the underlying venous or

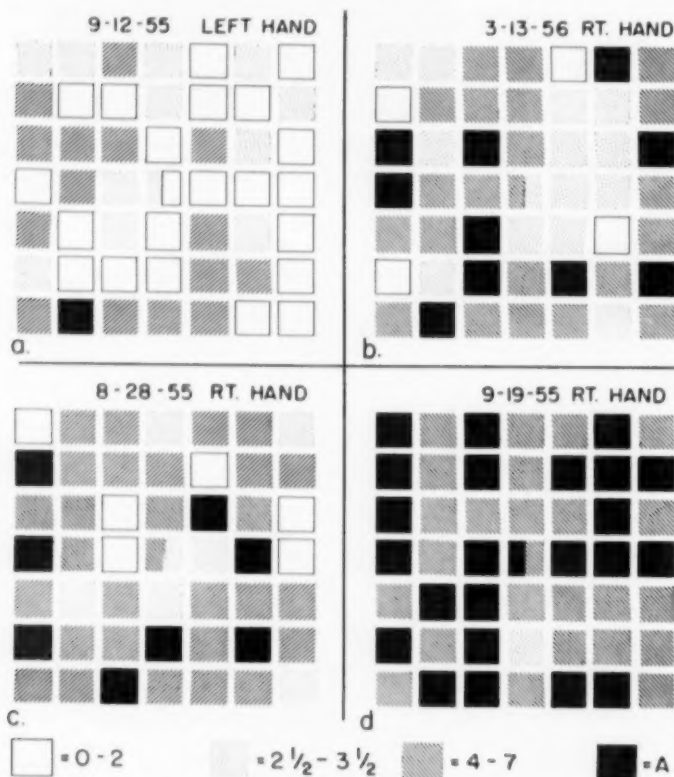


Fig. 3.—Charts of pain sensitivity illustrating the random nature of the pattern and the wide interindividual differences. (a) Subject 17; (b) Subject 7; (c) Subject 11; (d) Subject 9.



## Interindividual Variations in Pain-Spot Densities

Subject	Sex	Dorsum of Hand			
		Percentage Analgesic Areas in One or More Tests		Percentage Highly Sensitive Areas (Threshold of 2 or Less) in One or More Tests	
		Right	Left	Right	Left
1	M	40-58	34-58	0-14	0-24
2	F	50	58	12	6
3	F	34	20	4	0
4	M	20-24	24-40	4	2-20
5	M	24-26	16-36	0-4	0-2
6	M	8-20	16-24	12-26	0-8
7	M	20	16	8	12
8	M	8	36	38	12
9	M	6	32	10	0
10	F	26	10-20	2	6-22
11	M	8-16	4-14	2-14	6-26
12	F	8-12	2-8	16-34	34-38
13	M	10	2-8	10	8-14
14	M	2	8	10	14
15	F	0-8	0-2	0-52	4-44
16	M	8	0	24	48
17	M	2-4	2-4	34-50	28-44
18	M	0	0	86	56
19	F	2	0-4	14-22	26-34
20	M	0	2	100	92
21	M	0	0-2	82	70-78

bony pattern. This is well shown by the diagrams in Figure 3, which represents tests on the dorsum of the hand in four different subjects. Pattern *a* represents a subject with numerous low pain thresholds and rare analgesic spots; *b* and *c*, two subjects with intermediate patterns; and *d*, a subject with high pain thresholds and numerous analgesic spots. In nearly every subject studied the spatial arrangement of varied sensitivities appeared to be largely random. It could be shown that the distance between an analgesic and a highly sensitive spot is often exceedingly small. Hence, reinsertion of the needle into what was apparently the same puncture site often yielded a higher or lower threshold reading, presumably because the needle rarely reentered precisely the same spot.

Repeat tests of the same area on the same or other days usually gave similar scores, particularly in subjects in whom numerous tests were performed (Table). The results of five tests carried out over a four-month period on the dorsum of the left hand of one subject are shown graphically in Figure 4. The scores are all roughly comparable. In general, similar scores were obtained from right and left corresponding body areas of the same subject. In only one subject, a woman (Subject 15), were wide differences found on re-tests. In 10 tests, on

separate days, the percentages of highly sensitive spots varied between 0 and 52; her lower scores were made in the first four trials.

The unusually wide range of interindividual variation in pain-spot densities, as already alluded to (Fig. 3), is demonstrated further in the Table, where the percentages of both analgesic and highly sensitive areas are listed for all subjects tested. Since more than one test was usually carried out on any given hand, the range of percentages, rather

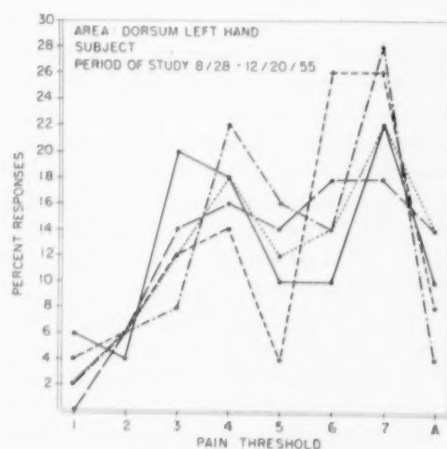


Fig. 4.—Graph to illustrate the similarity in patterns obtained from the dorsum of the left hand of the same subject (Subject 11) over a nine-month period.

than the average, is given. Among these subjects the percentage of analgesic spots ranged from 0 to 58, while the percentage of highly sensitive areas ranged from 0 to 100. No obvious correlation could be made between these variations among subjects and any visible or palpable differences in skin texture or thickness. A skin biopsy was made from one woman (Subject 3), who showed large numbers of analgesic spots. Microscopic examination of a section stained with the Holmes silver technique for nerve fibers revealed no unusual findings.\*

A mild to moderate ultraviolet burn of the test area in four subjects induced, as expected, a distinct depression of the pain thresholds. There was also noted a moderate decrease, but not a disappearance, in the number of analgesic spots, a result consistent with the morphological and biochemical changes of local inflammation.<sup>8</sup> In seven tests on four subjects a similar lowering of the pain thresholds was noted during the 12th to the 20th minute of neural ischemia by a brachial cuff, but analgesic spots persisted with but little change in their number, as compared with previous tests made in the same area.

Several miscellaneous observations were also made during the course of these experiments. Many subjects occasionally reported a sensation of cold, and less frequently of heat, at the pricked spot, as noted long ago.<sup>1</sup> These responses occurred both in pain-sensitive and in analgesic areas. A few subjects sometimes reported that the pain radiated beyond the actual point tested, a finding attributable perhaps to stimulation of an underlying cutaneous nerve. In a few tests a mild and fleeting "flash" of pain was noted as soon as the needle point made contact with the skin, presumably arising from transient deformation of a nearby pain-fiber ending. The "flash" was usually followed at some higher threshold by another pain which was more intense and

sustained; this latter phase undoubtedly represented closer contact of the needle point with a directly underlying pain ending.

### Comment

The different degrees of sensitivity to pain in any area explored with a needle point undoubtedly are closely related to the three-dimensional arrangement of the nerve nets in the epidermis and dermis. Spots of high sensitivity presumably indicate pain endings lying close to the surface, and less sensitive areas denote deeper endings. Sherrington's analogy of pain spots as lily pads scattered on and at varying depths below the surface of a pond is highly pertinent to these observations.<sup>9</sup> The analgesic spots might conceivably be interpreted merely to be areas in which receptors are present but have unusually high thresholds to excitation. If this explanation were true, an increase in neural excitability induced experimentally, as during the early phase of compression ischemia of a nerve trunk,<sup>10,11</sup> should reduce the number of analgesic spots, or even eliminate them. Our experiments yielded no such change. Hence, it is more tenable to consider the analgesic spots as minute areas of skin containing no pain endings, i. e., gaps in the "lily-pad" formation of pain receptors.

Anatomic demonstration that such analgesic spots are literally gaps in the pain-fiber network is as yet lacking. The solution must depend in part upon a histologic technique which will consistently stain all cutaneous nerve fibers and, in addition, identify pain endings as opposed to those carrying other forms of sensation. As Weddell has recently emphasized, present staining methods fail to make such accurate distinctions.<sup>4</sup> This same difficulty prevents any direct comparison of pain-fiber densities in the skin of persons with few and those with many analgesic spots.

The random nature of the spatial patterns recorded undoubtedly relates to the relatively coarse structure of the test grid. Analysis by an exceedingly fine grid, confined to an area of a few square millimeters,

\*The sections were prepared and examined by Dr. George Margolis, Department of Pathology, Duke University School of Medicine.

would presumably uncover the arrangement described by Bishop, in which scattered spots of high sensitivity are surrounded on all sides by areas of decreasing sensitivity extending outward.<sup>7</sup>

The finding that with unusually slow descent of the algesimeter the pain thresholds were lower requires consideration. It might be postulated that the usual rate was too rapid, so that the subject's response was delayed beyond the true end-point, thus yielding falsely high thresholds. However, the standard rate of descent of the algesimeter was made sufficiently slow to prevent this artifact. More tenable is the possibility that at a slower rate the needle causes more deformation or penetrates more deeply into the skin. Whatever the explanation may be, the factor of rate of insertion is clearly important in use of a needle algesimeter.

The most striking finding in this study is the wide person-to-person range of pain-spot densities. It appears at first glance to oppose the concept that cutaneous pain thresholds in man are fairly uniform. The principal support for this generalization, however, derives from the studies of Hardy and co-workers, who employed a technique of an entirely different order—a radiant-heat stimulus applied to a relatively wide area of skin.<sup>12</sup> Since spatial summation to pain has been shown not to occur, at least under the conditions of the heat-stimulus method, the threshold measurement thus obtained presumably applies to the most sensitive spots in the total exposed field. The densities of spots and the proportion which are analgesic are overlooked by such a technique. Hence, the conclusions reached by these two dissimilar methods of appraising pain sensibility are not incompatible.

The differing sensitivities to pain in any skin area tested by a needle have a practical as well as a theoretical significance. Despite the ample evidence for its existence, this variability is sometimes underestimated in clinical practice. It may lead the unwary examiner to conclude, after a cursory sensory examination in a neurologically normal

subject, that pain is distinctly better perceived in one limb area than in another; the discrepancy then disappears on more careful testing, in which several spots in each area are sampled in rapid succession, permitting the patient to "average out" the resultant sensation. This latter method, crude though it be, is therefore more serviceable in the clinical examination.

The potential value of the grid technique for sampling pain-spot densities in the diagnosis and study of early sensory nerve or tract lesions is yet to be adequately tested. This quantitative method is somewhat tedious and requires an alert subject able to make accurate judgments of sensory end-points. Its practical application in the clinic may therefore prove to be limited.

### Summary and Conclusions

There exists in normal skin a wide range of pain sensitivity to needle pricks, but the scores obtained from a given area in the same subject over a period of time are in general similar.

An unusually wide range of variation in pain-spot densities is found in interindividual comparisons. Analgesic spots varied from 0 to 58% in the test zones here reported.

An induced erythema of the test zone lowers the thresholds and causes a reduction, but not a disappearance, in the number of analgesic spots.

During the period of increased excitability of ischemic nerve (12th-20th minute of brachial compression), analgesic spots persist with but little change in number.

It is inferred from these experiments that the analgesic spot represents a gap in the fiber network rather than a pain fiber with an unusually high threshold.

These observations are relevant to apparent discrepancies which sometimes arise in routine sensory examination.

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## News and Comment

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### GENERAL NEWS

**Excerpta medica Lifts the Curtain on Soviet Medicine.**—As a result of plans initiated by the U. S. Public Health Service, National Institutes of Health, Department of Health, Education, and Welfare, arrangements have recently been completed with the Excerpta medica Foundation, 2 E. 103d St., New York 29, whereby, for the first time in the history of medicine, an extensive review of the Soviet medical literature in all areas of medicine will now be available to medical science in the United States.



## SECTION ON PSYCHIATRY

### Editorials

## Relation of Psychiatry to the Pharmaceutical Industry

These words are written as an individual, and not as the representative of any department or association.

Although a little learning is reputed to be a dangerous thing, a little too much understanding can be absolutely fatal. As psychiatrists we pride ourselves on this "understanding," claiming to neither condone nor condemn. The extension of this way of life outside the patient-doctor relationship can all too easily sap away righteous indignation. Overcontrol of aggressive and hostile forces in order to preserve the ego ideal of the all-tolerant, all-understanding, paternalistic psychiatrist can lead to blunting of social values. Some recent incidents call for strong feeling and immediate action.

Unlike most branches of medicine, the psychiatrist has had relatively little contact with the pharmaceutical industry until the past year or two. The advent of a new series of compounds with a \$150,000,000- to \$200,000,000-a-year market has opened a floodgate with which we were not entirely prepared to deal. The initial reaction of some of the unrealists was to have nothing to do with the hoard of strangers pounding at the gate. There was considerable resistance to accepting grants-in-aid, fellowships, and the usual type of financial support which the pharmaceutical industry has provided for specialists in other fields. The American Psychiatric Association, despite its lack of tradition in this area, has dealt with this both wisely and well by the judi-

cious acceptance of legitimate support. On the other hand, there have definitely been abuses, and it is these specifically which have occasioned the present editorial.

The contacts of psychiatry with the pharmaceutical industry have been so overwhelmingly beneficial that it would be well-nigh criminal to jeopardize them by not putting an immediate halt to the ill-advised attempts at exploitation and undue influence by a few scattered individuals in a minority of the drug houses. It is almost impossible to itemize in order of importance the salutary effects which can be noted. Certainly one of the most important was recently pointed out at the work conference sponsored by the Psychopharmacology Center of the National Institute of Mental Health by the editor of this journal. Although the remark was made in a somewhat different context, it is equally applicable here. This dealt with the awakened interest in both clinical and research possibilities in even the remotest of state, county, or city mental hospitals, because of the availability of these new methods of treatment.

The pharmaceutical industry has long ago learned the value of basic research and, in an effort to get at the fundamentals of drug action, has literally poured millions of dollars into this enterprise within the framework of their own organization. More important at this time than even the financial support is the availability of trained personnel in physical chemistry, biochemistry, pharmacology, animal psychology, and

medicine. The interchange of such trained persons between industry and the mental hospitals has already begun and will undoubtedly greatly increase as time passes. Both sides stand to gain a great deal.

The provision of grants-in-aid "with no strings attached" has provided an amazing transfusion of vitality into many a struggling clinical or laboratory research group in some clinic or state hospital. Financial watering of this apparently arid region has resulted in the appearance of oases which help to nourish the whole surrounding psychiatric neighborhood. The university departments of psychiatry and neurology have similarly benefited and, in turn, contributed to the greatly expedited attack on the problem. Nor has the research supported by the pharmaceutical houses been limited to clinical testing in the area of biochemistry. Physiological, psychological, and even psychoanalytic projects have been supported. More than one company has adopted the philosophy "What is good for the field of mental health is ultimately good for us." Without exception the pharmaceutical houses have been most generous in providing free supplies of pharmaceuticals until the value of a particular compound has been well established. In addition, they have provided placebos, prepared medications in the form that the researcher finds most convenient, and provided adjunctive pharmaceuticals and numerous other such "small services." Even with those preparations whose saleability has been well demonstrated, free supplies are usually available for a new or badly needed clinical application.

Both direct and indirect support have been given to the major organizations in the field of mental health. There have been not only contributions to general budgets but the provision of fellowships and the support of meetings which bore no relationship to pharmaceuticals per se. There has been no attempt of which I know to direct the selection of applicants for such fellowships or to determine the subjects or

composition of such meeting, with the exceptions indicated below. The pharmaceutical houses have served a potent role as disseminators of information. Their publications have carried articles on progress or opinions in respect to mental illness which by no means deal exclusively with the beneficial effects of the particular preparation which they may happen to market. By underwriting the cost of publication they have made a whole variety of reports on current progress readily available. When these have dealt with pharmaceuticals, the negative opinions and the value of competing products have been freely presented, since no attempt was made to influence editorial policy. A fair number of the publications so supported in no way dealt with the pharmaceutical area.

The most recent benefit of this general type has been the offer of one of the pharmaceutical houses to underwrite, for five years, expenses for bringing a distinguished foreign researcher to the United States for presentation of a lecture at the annual meeting of the American Psychiatric Association. The choice of person would rest with the Association. In summary, the pharmaceutical houses have provided an infusion of funds, of personnel, and of general helpfulness, in addition to the specific merits of the products which they are producing.

Now, as to the other side of the picture. Most of the difficulties arise from over-eagerness on the part of the pharmaceutical houses to push their particular product. In occasional cases a physician has encouraged a pharmaceutical house to pander to his need for recognition and allowed himself to be exploited. One brazen incident of this type resulted in premature, unwarranted claims which served only to bring disrepute to the whole field of pharmaceutical investigation. Acceptance of financial support or assistance, the provision of free medication, or other help should not place the recipient under a feeling of obligation that he must produce a "favorable" report. Short-term gains of this sort are rapidly



dissipated, since after one or two such unsubstantiated testimonials the investigator finds his professional integrity is discredited, the journals find his publications no longer acceptable, and even the pharmaceutical houses allow him to drift into the discard. There exist certain investigators, in all the fields of medicine, who are known to turn out laudatory articles about whatever they investigate (whether the deception is conscious or unconscious), and these are generally dislaid by the drug industry.

Before I continue, a point of major clarification is needed. One cannot speak of "pharmaceutical houses" as though it were a single, integrated functioning entity. Like Brahma, most of them are four-handed, four-headed personalities in which centralization of control is not always perfect, so that not infrequently there is incoordination between one arm and another. The two hands with which psychiatrists are most likely to come into contact are Research and Sales and Promotion. These have quite different functions and often quite different ethics. With very few exceptions, the research divisions of the pharmaceutical houses not only are sympathetic and understanding of the problems which the investigator or clinician faces but are interested in a completely impartial report, although naturally they are hopeful that the drug under investigation will prove to be a valuable one. Certainly the legitimate pharmaceutical house prefers honest negative reports, especially early in the investigational stage, since it can then abandon the product rather than invest hundreds of thousands of dollars, only to find its uselessness when it is placed on the competitive market.

In contrast, the function of Sales and Promotion is exactly what its name implies. Their basic concern is not judgment as to the value of a particular preparation but the task of promoting and selling what is provided them. The limitations and side-effects of a particular preparation are provided them by the clinical investigation

division of the pharmaceutical house, but by the time the information has passed from the original investigator to the research or clinical investigation division, then on to the top echelon in Sales and Promotion, and down through the field managers and out to the detail men an inevitable process of oversimplification, with the tendency to "accentuate the positive and eliminate the negative," results. Many of the detail men themselves are extremely conscientious and attempt to keep abreast of the current literature in its original form, but unquestionably certain distortions result. As has been pointed out to me, the pharmaceutical industry is unique in that the advertising and sales promotion are directed at the physician; the actual purchasing is done by the wholesale houses, the ultimate consumer, the patient, not having direct relationship with the manufacturer or producer. This in itself produces a highly complicated situation. Although the Sales and Promotion divisions of most of the pharmaceutical houses operate at a much higher ethical level than do most businesses, they nevertheless exist in a highly competitive market and cannot help being influenced by the successful practices of other types of merchandising. It is in this area that conflict between commercial techniques and professional standards may arise.

Nowhere have the characteristics of a profession been expressed more succinctly than in a recent article in *Science* by Vannevar Bush. He says in part:

Members of a profession minister with dignity; they demand the respect due to their skill and devotion; they do not merely advise, they insist upon being heard; they do not submit their opinions for the judgment of the layman who is their client, no matter how powerful he may be; they insist that they have his confidence and that, in their special field, their opinion shall control, or that the client turn elsewhere. They recognize that he may need to join their findings with factors outside their special field in coming to decisions. . . . But within their proper scope, modest men though they may be, they advise and guide with pride, and with the insistence that the ancient art which they represent be received with the respect which is its due.

It is exactly at this point—the insistence that medicine be received with the respect which is its due—that there is the necessity of speaking out. It is the business of business to make a profit, but unless the profession insists upon its own rights and privileges it will find itself being manipulated and exploited for ends which are not its own. Both business and the profession have their proper area of activity and, like good neighbors, get along best when each has clearly defined what is within its own sphere and, if necessary, demonstrated that it will not be cajoled or maneuvered.

In a number of petty ways there have been attempts at infringement upon professional prerogatives. By bringing these to public protestation, the best interests of both groups will be served, since then the profession can retain its dignity and the commercial interests not be tempted to operate in an area that is beyond their proper scope. The list of attempted abuses is presently rather small but is apt to grow in both length and magnitude unless the line is drawn. Whereas it is perfectly appropriate for a pharmaceutical house to encourage an investigator to report positive favorable results if the investigator is satisfied that he has tested a sufficient number of cases in an adequate manner, it is equally improper that any attempts should be made at suppression of an article containing an unfavorable report. It is consonant with professional dignity for an author to allow himself to be quoted if his words are not torn out of context to say something other than he intended, but it is disturbing to discover one's self quoted in a manner which implies recommendation of a product when it may have been given only "faint praise" as compared with other drugs. Scientific reports are not to be used like play reviews, where the few kindest words are plastered on a billboard or in a newspaper ad. There is certainly nothing immoral about sending the draft of an article dealing with a drug to the appropriate pharmaceuti-

cal house for comment which may provide information unknown to the author (published or unpublished), but it is certainly below professional dignity to have the pharmaceutical house write the article, to which the investigator merely affixes his signature. The practice of collecting such and such a number of cases, paid for at so much a head, is at least questionable. There exist certain rationalizations for doing this, but the value of forms hastily filled in by busy clinicians is not a sensible way of evaluating a drug.

All of the above-mentioned incidents have occurred within the past year, and the ones that I have itemized were deliberately selected because they had occurred to persons other than myself. There have been different, equally undesirable, occurrences, against which I and others have had to take a firm stand and issue a strong protest.

Since it now appears happily inevitable that psychiatry and the pharmaceutical industry will be closely associated, the problem is how best clearly to define the rights and prerogatives of each. To this end we (and I serve merely as the spokesman for most of my colleagues who are doing clinical drug investigations) believe that a conference of a group of such investigators with the top administrators of the pharmaceutical industry would serve the valuable purpose of establishing certain "ground rules" which would make for a happy and compatible relationship in the future. After such a meeting I believe it would be desirable for the American Psychiatric Association to establish an *ad hoc* committee to deal with infringements against the to-be-established ground rules so that the force and dignity of the entire profession might be brought to bear against those who attempt to violate these ethics.

There should certainly be no attempt to regiment by whom and in what way clinical investigations should be done, but since the number of investigators in this field is relatively limited compared with those in many other fields of medicine, it is believed that

agreement could be reached on such subjects as the use of scientific publications for sales and promotion, the "leaking" of information to the press prior to presentation at a professional meeting or in a professional journal, and other obvious areas of this type which call for discussion.

My personal familiarity with the men who serve in the pharmaceutical industry in both professional and administrative capacities is reasonably extensive, and, with few exceptions, I know them to be men of good will, whose interest extends beyond the purely financial to a strong desire to be of service not only to the medical pro-

fession but to mankind in general. Unless we bring to the attention of this ethical and well-intentioned group the rare exceptions, it will be impossible for the necessary moral suasion to be exerted, and they, too, may find themselves debased by attempting "to meet competition."

The negative criticisms which I have had to offer are few compared with the multiple benefits, but I believe action must be taken promptly and effectively in order to maintain that which is begun so promisingly.

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# Effects of "Tranquilizers" upon Pathological Activity in Psychotic Patients

## *I. Chlorpromazine*

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Delay, Deniker, and Harl<sup>1</sup> were first to use chlorpromazine as a single agent in the treatment of excited and agitated states and to note its quieting effect upon such psychiatric conditions. Excellent descriptions of the "tranquilizing" effects of chlorpromazine have been reported by European and English investigators.<sup>1-4</sup> In some of these reports it appears that "tranquilizing" effect refers merely to the substitution of somnolence for "pathological activity," while in others it seems that "normal" supplanted "abnormal" activity. Sometimes abnormal activity was defined as "hyperactivity" and sometimes as "hypoactivity." In the American literature emphasis has been placed on the reduction of hyperactivity.<sup>5-7</sup>

Although almost all evaluations of chlorpromazine in psychiatry have attempted to measure its effect in terms of changes in disturbed behavior, few investigators have actually defined in advance the specific abnormal behavior to be observed and then tested their data statistically to see whether specific changes in such behavior occurred when the drug was given. Most studies have not been adequately controlled, and in only a few have precise measurements of drug-induced changes been attempted. Seldom have the criteria of disturbed behavior been expressed in observable symptoms of demonstrable reliability. Most investigators

agree that the drug causes a marked reduction in pathological "overactivity," but they seldom have stated clearly what replaces this behavior.

The purpose of the present study\* was to evaluate the effects of chlorpromazine upon pathological activity in psychotic patients when pathological activity was defined in terms of specific behavioral signs and when degree of activity was quantified by actual count of the number of times per week these signs appeared. It was also proposed to observe the relationship between activity and somnolent behavior and to study changes in this relationship induced by chlorpromazine. A method which was found to be useful in defining and quantifying pathological activity will be presented in considerable detail.

## Materials and Methods

*Observers.*—Nine male psychiatric aides, with an average of 8.2 years of experience in handling psychiatric patients, served as observers. Instruction was given in making observations, but the aides were not informed of the drug being tested or told which patients received the drug or the placebo. One of us (R. P. C.) held a one-hour interview with each observer at the conclusion of the experiment. The interviews were focused upon the observers' attitudes about the use of drugs in psychiatric treatment, their hopes for results, their opinions about the drug tested, and their feelings about such experiments. All of the observers were optimistic about the drug, and all held great hopes

\* The members of the nursing service served as observers; Miss Ann Mathews, director of nursing, and Mr. Ernest J. Sinnacher, chief pharmacist, assisted in this study; Dr. Harris Hill of the Addiction Research Center helped with the experimental design.

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## CHLORPROMAZINE EFFECT ON BEHAVIOR

for therapeutic success by this means. They openly encouraged the patients to cooperate.

**Subjects.**—Twelve chronic schizophrenic male patients, ranging in age from 27 to 64 years, who had shown daily behavioral signs of "pathological activity" over a period of at least three months were selected. Two were of the catatonic type; two, of the hebephrenic type; one, of the undifferentiated type, and seven, of the paranoid type. Length of illness ranged from 3 to 44 years, with an average duration of 16.6 years. During the course of their illness, all patients had received ECT and insulin therapy, and two had undergone lobotomy five years prior to the study. None had received any therapy beyond ordinary institutional care for three years prior to the experiment.

**Drugs and Doses.**—Except in two instances, in which the drug was initially administered intramuscularly, chlorpromazine was given orally. The initial dose was 50 mg. every six hours and was increased over a four-day period to 150 mg. every six hours (600 mg. daily). Placebos used were identical in appearance with the chlorpromazine.<sup>†</sup>

**Experimental Design.**—The 12 patients were divided into two groups of 6 by a disinterested, non-participant pharmacist. After a control period of three weeks, in which neither group was given placebo or chlorpromazine, one group received chlorpromazine for six weeks, and the other group received placebo. During a second period of six weeks, both groups were given placebo. During a third period, the group which had started on placebo was given chlorpromazine for six weeks, and the other group was given placebo. Only the chief pharmacist knew which patients were on chlorpromazine or placebo at any given time. Thus, a "double-blind," cross-over design was used in which each patient served as his own control.

**Measurement of Pathological Activity and Sleep.**—Pathological activity was defined as those symptoms of motor activity peculiar to each patient as revealed by a review of his medical chart over a period of two months prior to the experiment. These behavioral symptoms were supplemented by one month of direct observation of each patient by psychiatric residents and ward nurses. The psychiatric aides were instructed by one of us (R.P.C.) until all consistently recognized the specific symptoms exhibited by each patient.

A behavioral grading chart was prepared for each patient in the study, consisting of a face sheet, on which his characteristic symptoms were listed and numbered, and weekly score sheets. The score sheet was constructed with 7 columns (one for each day of the week), and 24 rows (one for each hour of the day). The aides were instructed to

observe each patient hourly and to note in the appropriate space on this score sheet the number-symbol of the symptoms listed for that patient which appeared during the hour. If no pathological symptoms appeared, a zero was entered. If no observation was made during a given hour, a line was drawn through that space of the score sheet. The observers also recorded on the face sheet any new recurring symptoms of pathological behavior.

The degree of pathological activity exhibited by each patient was determined by counting the number of hours per week in which one or more of his characteristic symptoms were observed. In computing daily pathological activity scores, the hours between midnight and 6 a.m. were omitted because of almost complete absence of pathological activity during this period.

Standard sleep charts with spaces for entries every half-hour for all 24 hours of the day were filled in on each patient, starting in the third week of the control period and continuing throughout the experiment. A sleep score on each patient was obtained by counting the number of hours during the week when the patient was asleep.

Direct comparisons between pathological activity and somnolence were made by converting their raw scores into "standard deviation units," using the control data as the standard. Statistical significance of mean changes induced by chlorpromazine in both pathological activity and sleep was tested, using the *t*-test as applied to repeated measurements on the same subjects.\*

Of special interest was the relationship between sleep and pathological activity during the hours of the day when the patients were normally awake. The relationship of sleep and pathological activity scores during the intervals of 8 to 11 a.m. and 1 to 4 p.m. was statistically computed, using appropriate analysis of variance and covariance techniques.\*

**Reliability of Pathological Activity Scores.**—During the initial three weeks observers were given additional training and practice in the recording procedures. This period also provided an opportunity to estimate the stability of the activity scores. Means and standard deviations were computed to establish the level of pathological activity, individual differences in activity levels among subjects, and weekly fluctuation of activity scores.

In order to test interobserver reliability, two or more aides independently observed all patients during three two-week intervals, spaced throughout the experiment. Rank-order correlations\* among observers were computed to test the reliability of the over-all score. Extent of agreement between observers on specific behavioral symptoms was also tested.

**Clinical Laboratory Procedures.**—During the control period the following observations were ob-

<sup>†</sup>Chlorpromazine was supplied through the courtesy of Mr. Theodore Wallace, Smith, Kline, & French Laboratories, Philadelphia.

tained: blood pressure (sitting), urinary urobilinogen (Ames' Ictotest Paper), and complete blood count. Throughout the experiment, the following determinations were repeated, as follows: weight, once a month; urine urobilinogen, once a week; complete blood count, every two weeks, and blood pressure (sitting), one-half hour after each dose of medication and placebo.

**Follow-Up Study.**—Upon completion of the experiment, all medication and observations were interrupted for 10 days, after which they were resumed for 6 weeks, in order to obtain data on any residual effects of the drug and to observe further the effects of placebo and attention upon pathological activity. Two groups of six patients each were used. Each group was composed of three subjects from each of the experimental groups employed in the major study. One group was given placebos and all the attention (including clinical procedures) given in all 18 weeks of the experiment. The other group was denied placebos and attention. After three weeks the groups were crossed. Differences in pathological activity and sleep among these various groups were computed and tested for statistical significance.

## Results

**Reliability of Pathological Activity Scores.**—Statistical analyses of pathological activity scores during the control period are presented in Table 1. Fluctuation in group averages from week to week was

TABLE 1.—Means and Standard Errors of Weekly Pathological Activity Scores During the Control Period

Patient No.	First Week	Second Week	Third Week	Mean per Patient
1	58	51	47	42.0
2	79	72	73	74.6
3	46	56	60	54.0
4	45	57	41	47.6
5	90	106	102	99.3
6	66	82	80	76.0
7	87	103	98	96.0
8	72	75	83	76.6
9	81	93	83	85.6
10	72	78	52	67.3
11	80	75	65	73.3
12	72	94	81	82.3
Mean per week	70.66	78.50	72.08	73.7
S.E.M.	6.94	5.23	5.60	4.25

statistically negligible. These analyses showed that the least active patient during the control period had an activity score of 41 and performed at a level which was almost six times the largest standard error (6.94). Pathological activity scores were therefore sufficiently elevated and stable enough at the beginning of the experiment to permit measurement and statistical testing of changes induced by drugs.

Direct evidence of reliability of scores was obtained by comparing the observations of multiple observers who independently scored all patients for pathological activity. Rank-order correlations<sup>8</sup> among observers

TABLE 2.—Distribution of Signs of Overactivity Graded Among Twelve Psychotic Patients

No.	Overactivity Sign Rated	No. of Patients in Whom		
		Sign Appeared	It Was Chief Symptom	It Was "Fringe" Symptom
1	Almost constant crying, laughing, garbled talk	10	1	0
2	Belligerently uncooperative and negativistic	4	—	4
3	Tears up paper	3	1	2
4	Spits on floor or furniture, rubs with hand or foot	1	—	1
5	Faces floor	6	5	1
6	Actively refuses food	2	—	2
7	Runs from place to place	2	—	1
8	Dances	1	—	1
9	Sits rocking back and forth on bench	1	1	—
10	Masturbates overtly	1	—	1
11	Hostile, abusive language to patients and/or nurses	2	2	—
12	Repetitiously draws or prints letters and numbers	1	—	1
13	Assaultive toward patients and personnel	3	—	3
14	Picks at skin	1	—	1
15	Picks up dust or tobacco particles	1	—	1
16	Throws articles out of window	1	1	—
17	Throws food tray	1	—	1
18	Works "on the run"	1	1	—
19	"Cleans" borders of corridors or bathrooms	1	1	—
20	Grinds teeth	1	—	1
21	Aggressively sweeps with broom	1	—	1
22	Beats head with fists	1	—	1
23	Teases other patients	1	—	1
24	Messily plays with food	1	—	1
25	Plays "games" with other patients	1	1	—
26	Makes homosexual advances toward other patients	1	—	1
27	Destructive toward equipment (plaster, radio, etc.)	1	—	1
28	Almost constant inappropriate grinning	1	—	1
Total		52	14	39



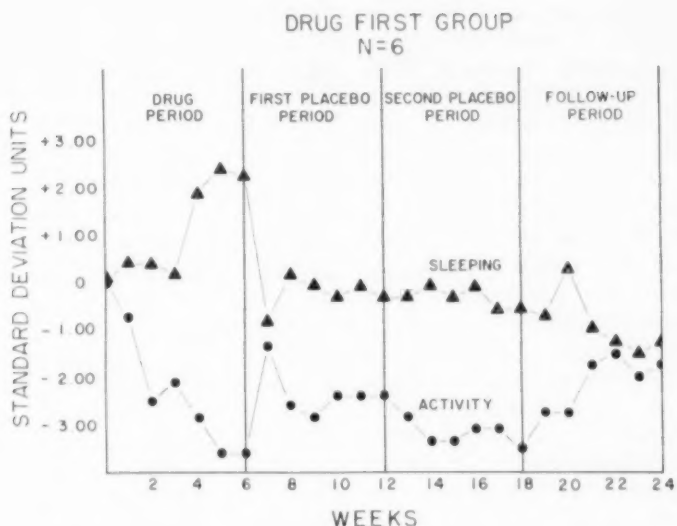


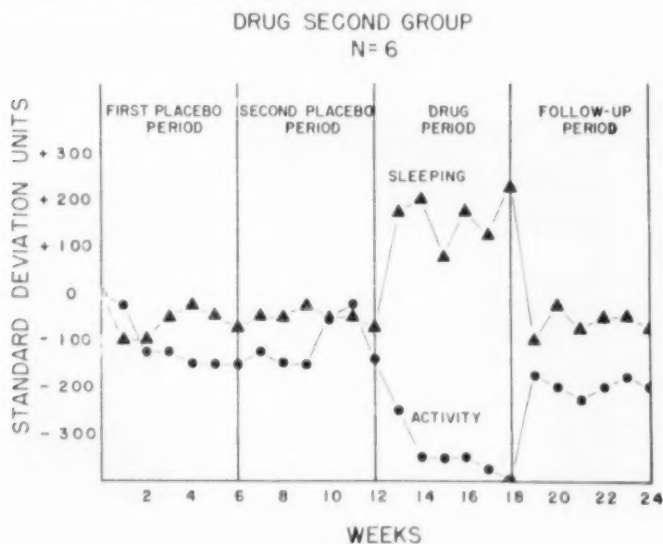
Fig. 1.—Mean changes in pathological activity and sleep induced by chlorpromazine in first drug group (N=6).

ranged from 0.61 to 0.98, with a median  $\rho$  of 0.90. These coefficients satisfied the usual standards of reliability of measurements.

Analysis of specific behavioral symptoms showed that the number of different symptoms which characterized individual patients ranged from 2 to 6, with a mean of 4.5.

The total number of symptoms listed for all subjects was 52. There was, however, a strong tendency for observers to agree upon a single symptom for each patient. For example, they consistently noted 14 of the 52 symptoms (Table 2). The remaining 38 symptoms were not consistently observed

Fig. 2.—Mean changes in pathological activity and sleep induced by chlorpromazine in second drug group (N=6).



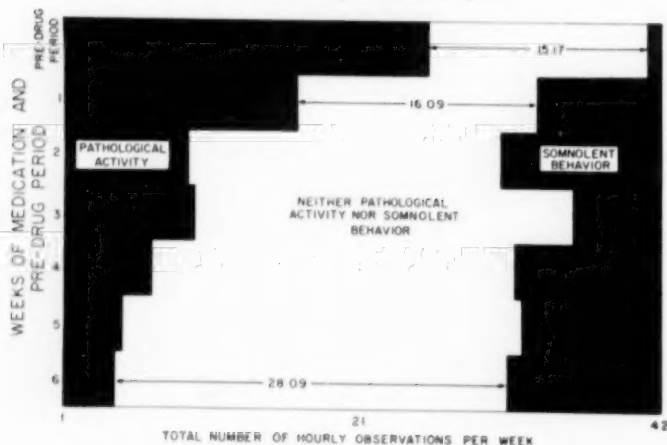
by multiple observers and may be considered "fringe symptoms," which, from the standpoint of measurement, represented inconsistent fluctuations in the patients' behavior. The 14 symptoms upon which the observers agreed, while representing less than one-third of the number originally "defined," accounted for 75% of the total pathological activity observed during the experiment.

**Changes in Pathological Activity and Sleep Induced by Chlorpromazine.**—A marked reduction in pathological activity followed chlorpromazine. In both drug periods activity dropped significantly below the predrug levels by the end of the second week of medication. In the first drug group (Fig. 1), there was a mean reduction of 2.53 standard deviation units in hours per week of pathological activity. In the second drug group (Fig. 2), there was a mean reduction of 2.25 standard deviation units. In both instances these changes were statistically significant ( $P < 0.01$ ). After abrupt cessation of the drug, pathological activity rose sharply during the first week but did not regain the predrug level. In fact, activity scores in the first drug group did not reach the predrug level until more than three months after the last medication.

In both groups (Figs. 1 and 2) reduction in pathological activity was accompanied by increase in hours of sleep. After abrupt cessation of the drug, mean hours of sleep returned to the predrug level during the first week.

**Drug-Induced Changes in Sleep and Pathological Activity During Waking Hours.**—Statistical analyses of pathological activity and somnolent behavior observed during hours of the day when patients are normally awake are presented in Fig. 3. Since both sleep and pathological activity were limited to "normal" waking hours (42 weekly), scores theoretically could range from 0 to 42. During the control period, the mean pathological activity level for all patients was 25.33, and the mean sleep score was 1.50. In the first week of medication, the mean for pathological activity dropped to 16.41, but the mean hours of sleep rose to 9.42. Hours of the day when neither pathological activity nor sleep was observed (Fig. 3, white area) increased from 15.17 to 16.09, a statistically negligible increment. As medication was continued, hours of pathological activity were progressively fewer, whereas hours of sleep increased very little after the first week on the drug.

Fig. 3.—Drug-induced changes in sleep and pathological activity during waking hours.  
Pathological activity significantly reduced  $P < 0.01$ .  
Sleep behavior significantly increased  $P < 0.01$ .  
Symptom-free behavior significantly increased  $P < 0.01$ .



Consequently, hours of symptom-free behavior increased progressively, from 15.17, in the first week on drug, to 28.09, in the sixth week on drug.

Both the reduction in pathological activity and the increase in hours of sleep were statistically significant ( $P < 0.01$ ). However, analysis of covariance demonstrated that the increase in sleep during waking hours was not sufficient to account for the decrease in pathological activity observed during the same period.

*Side-Effects.*—No significant changes were observed in body weight, blood pressure, liver function studies, or blood counts during the experiment. In two cases a mild skin rash was observed over a brief period.

After receiving the drug for two weeks, one patient who had received 600 mg. daily for seven days showed signs of severe Parkinsonism, which disappeared five days after the drug was stopped. The patient also had a pulse rate of 148/min. and a respiratory rate of 32-36/min. After being off drugs for 10 days, his dosage was again increased to 600 mg. per day for seven days. Signs of Parkinsonism reappeared, but disappeared during the six weeks he was receiving placebos.

*Follow-Up Study.*—No significant effects of attention (placebo) upon pathological activity or sleep were observed during the follow-up period. Sleep scores remained constant at the predrug level, and activity tended to revert to the control period base line.

### Comment

The findings raise some questions which may be answered by future studies. The level of pathological activity in the group which received chlorpromazine first remained significantly below its predrug base line for three and one-half months after the drug was stopped. Presumably, the group which received chlorpromazine second would have behaved in a similar way had observations been continued for more than six weeks. The results in the first group suggest a possible "carry-over" effect of

longer duration than other studies have shown. Furthermore, the fact that drug-induced somnolent behavior during waking hours tended to increase as pathological activity decreased suggests that the drug may, in part, cause substitution of one form of pathological activity for another. It is felt that future studies should define and analyze the drug-induced behavior that replaces the behavior which is reduced or abolished.

Several investigators have suggested that the expectations of observers who administer the medication may materially affect the results of the drug. Sabshin and Ramot<sup>9</sup> attributed the lack of success with chlorpromazine in their study to the pessimism of the personnel who participated in the experiment. Elkes and Elkes<sup>4</sup> attributed improvement in the control group in the first three weeks of their experiment to the positive attitude of the personnel. The importance of the observer's attitude has been perhaps, overemphasized. Observers in this study were highly optimistic and expected beneficial effects from the drug. During the first two weeks of the experiment pathological activity in the placebo group dropped slightly but not significantly. Since placebos and "attention" by observers had no significant effect upon pathological activity during the follow-up period, it is questionable that the initial decline in the placebo group was attributable to the attitudes of the observers. It could have been due to the over-all reduction in extraneous stimulation of the placebo group, resulting from the lowered pathological activity in the drug group.

The procedures used to quantify pathological activity in this study offer certain advantages over the usual approaches reported in the literature. Defining the specific behavioral symptoms peculiar to each subject under observation in advance, and training observers to recognize these signs consistently, reduces subjectivity in the observations. Pathological activity was expressed as a numerical score that could be statistically tested.

The particular behavioral symptoms isolated in this experiment were specific to the subjects studied. There is no reason to expect these same symptoms to appear in other subjects under other conditions. It is suggested, however, that the method described in this paper can be applied to the study of drug effects under a variety of conditions and with different types of subjects.

### Summary

In a "double-blind" experiment, the effect of chlorpromazine on "pathological activity" and somnolent behavior was studied in 12 chronic psychotic patients. Selected symptoms of pathological activity peculiar to each patient were noted hourly by nine psychiatric aids over a period of 28 weeks. Half-hourly sleep charts were kept over the same period.

Use of 600 mg. of chlorpromazine daily significantly reduced pathological activity in these psychotic patients. The drug also significantly increased somnolence during hours of the day when these patients were normally awake, but this increase was not sufficient to account for the reduction in pathological activity.

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# Consequences of Surgical Illness and Treatment

## *Interaction of Emotions, Personality, and Surgical Illness, Treatment, and Convalescence*

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The commonest sequence in surgical practice may be described in four words: illness, treatment, convalescence, and recovery. The present paper reports a study of the natural history of these four processes in 200 surgical patients. Further, it reports an exploration of the interaction of these processes with the total personality and of the pathways by which psychological factors modify the patient's transition from illness to recovery and by which personality is changed in the surgical experience.

Previous publications covering the work of our research team have reported the prevalence of psychiatric disorder in surgical patients, the relationship of emotional conflict to the onset of surgical illness,<sup>1</sup> the problem of psychoses during surgical illness,<sup>2</sup> special psychological problems involved in the treatment of the aged with surgical illness,<sup>3</sup> and the phenomenon of delay in seeking surgical diagnosis and treatment.<sup>4</sup>

### Method and Methodologic Problems

The research was planned and executed by a multidisciplinary team, including surgeons, psychiatrists, psychologists, social case workers, a

philosopher,\* and a sociologist.† We settled upon broad aims, directing our efforts toward a more complete understanding of the psychiatric and social problems of a representative group of municipal general hospital surgical patients during the period of illness, treatment, and convalescence. We devised a procedure for the random selection<sup>5</sup> of 200 patients admitted to the wards of the surgical service during a single calendar year. At the end of the year we compared the patients who had been included in the study with the entire surgical population (3656) of the same year. The two groups were quite similar with respect to age, sex, duration of hospital stay, site, and severity of surgical illness and whether or not operation was performed. Thus the 200 subjects were found to be "representative" of the larger group of patients admitted during the year.

There were almost daily psychiatric interviews of the randomly chosen subjects from the day of admission until leaving the hospital. Interviews varied in approach and form and were not rigidly preconceived. While adapting our interviewing techniques to the individual patient, we made an effort in each case to record a longitudinal history proceeding from earliest memories to the current situation and covering childhood, adolescence, sexual experience, marital life, vocational experience, and interpersonal relations. Our purpose was to formulate the person's characteristic defenses against anxiety, neurotic or otherwise; the proneness to anxiety and depression; behavior under stress, and the reactions to the present illness and previous similar episodes.

Some comments, first, on the research process itself are in order. We found that the distress of major illness did not in all cases enhance the desire or ability of the person to communicate his feelings and life history, though despair in such a situation might loosen a usually taciturn person. Though the subjects were informed that they were

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participants in a study aiming to understand and perhaps remedy certain problems of surgical patients, our visits stirred suspicion and guarding in many. Some patients thought that the researchers were investigators for the welfare department, the police, or the Federal government in spite of active assurance to the contrary and repeated explanation. When the patients did comprehend our intentions, many still resented the intrusion, especially when the subjects felt they had to mobilize every resource against the threat of illness and death and believed they could spare no extra energy for our purposes.

One of the realities of psychiatric research in a clinical setting is that the human being who may become a research subject is seldom motivated to fit himself into the rigors of research design. Because he has a life to live and is motivated by self-interest, he may become unavailable for "follow-up," or, because he had a severe illness, he may die during hospitalization or shortly after leaving the hospital. Of our 200 patients, 72% were seen in follow-up; we were unable to see 28% of our patients three to six months after discharge from the hospital. The subjects who were not observed after convalescence included 15% who died either in the hospital or within the interval between discharge and the time for follow-up and 13% who could not be located, refused to return, or actively fled from contact, though every resource offered in a large city was employed by an energetic and persistent social case worker. The follow-up patients did not include only those pleased with the hospital or submissive and anxious to please the researchers. Some patients came in to express exasperation with regard to our persistence and to put an end to our relentless invitation.

The loss of contact with some patients or the death of others in the original sample could tend to alter the characteristics of the group under study in a direction away from randomness and toward selectivity. We have compared the patients seen in follow-up with those who were not seen with respect to the degree of hazard experienced in operation, as judged by a surgeon.

Figure 1 shows that, when the total group of 200 patients is divided into those dying before follow-up contact, those unavailable for contact, and those seen in follow-up, there are no significant differences in the three groups with respect to degree of hazard of operation.

Table 1 gives values of probability ( $P$ ) to indicate the significance of difference of certain other characteristics of the random group of 200 compared with the total surgical admissions during the same year. It may be seen that the random group is highly representative. In the other column the significance of difference from all surgical admissions is given for the follow-up

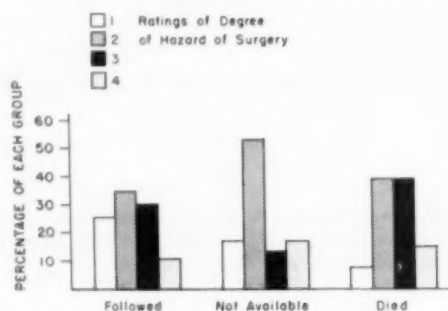


Fig. 1.—Severity of operation (degree of hazard) in patients followed, those unavailable, and those who died. Each patient was rated on an ascending four-point scale for the degree of severity of operation according to the degree of hazard the procedure entailed. The histogram shows the percentage in each group, those followed, those unavailable for follow-up, and those who died, rated 1, 2, 3, and 4 for the severity of their respective surgical procedures.  $\chi^2$  analysis of the differences in distribution showed them to be not significant.

group. The follow-up group was not significantly different from the total surgical admissions except with respect to sex (proportionately more females) and with respect to whether or not an operation was performed (proportionately more operations). In our opinion these significant differences do not affect the type of conclusions reached in the present report.

A comparison of the male-female ratios is as follows:

	Total Group	Random Group	Follow-Up Group
	(3656)	(200)	(144)
M/F=	1910:1746	98:102	64:80

Since our study emphasizes the evaluations of the patient's psychiatric status at various stages of the process of "illness, treatment, convalescence,

TABLE 1.—Similarities and Differences of Initial Random Group (200) and Follow-Up Group (144) Compared with Total Admissions (3656) for Year\*

	Random $P$	Follow-Up $P$
Age	0.60	0.70
Race	0.70	0.20
Sex	0.30	0.05 †
Hospital duration	0.20	0.30
Operation or no operation	0.40	0.02 †
Degree of severity	0.20	0.20

\* The initial randomly selected group (200) and the follow-up group (144) were compared by means of  $\chi^2$  with the total surgical admissions (3656) of the same year with respect to some relevant variables. Indices of probability ( $P$ ) are listed to show the significance of differences.

† Variables for which there were differences significant at the 5% level or better than the 5% level.



# SURGICAL ILLNESS—ADJUSTMENT

and recovery," some comments are in order about the ways of dealing with the data derived from psychiatric examinations.

In order to draw conclusions about changes in psychiatric status during the course of surgical illness, we planned to compare the initial psychiatric evaluation with the psychiatric picture found on the follow-up, using a number of criteria of change. We started with a general comparison of the change in psychiatric status after surgical treatment with the status before—a comparison based on our data on the patient's history, the cross-section view of the personality formulated during the hospital stay, and repeat observations after convalescence.

The more specific operational criteria for evaluating change in psychiatric status can be summarized as follows:

1. Change in frequency and severity of neurotic symptoms, such as free anxiety, phobias, depression, and dissociative reactions. Appearance of new neurotic symptoms.
2. Change in disabling attributes of character, rigidity of attitude, or behavior that made adjustment in vocation, marriage, or society notably difficult. Appearance of new character or behavior disorder.
3. Change in psychotic or borderline psychotic symptoms. Appearance of new psychotic symptoms.

## Psychiatric and Surgical Results of Surgical Treatment

The changes in our series of patients, in both psychiatric and surgical status from the time of admission to the hospital to the time of follow-up, are summarized in Table 2. It will be noted that we had sufficient information to evaluate change in 128 of the 144 patients who were seen three to six months after discharge from the hospital. There were nine possible groups or combinations of psychiatric and surgical evaluations into which the subjects could be distributed by the rating method. Table 2 demonstrates that the cases are actually concentrated in five of the nine groups. A statistical procedure ( $\chi^2$ ) shows that this particular distribution is not random but is significant at the 1% level, and consequently there was a significant relationship between the course of surgical treatment, on one side, and changes in personality adjustment, on the other. This finding of a significant relationship between psychiatric and surgi-

TABLE 2.—Changes After Convalescence in Psychiatric and Surgical Status of the 128 Patients on Whom Information Was Sufficient to Make an Evaluation\*

Surgical Status	Psychiatric Status			Total
	Improved or Continuing Adjustment	Persisting Maladjustment	Worse Adjustment	
Improved	A 28(87.5%)	B 33(67.4%)	C 29(61.7%)	90
Stationary	E 1(3.1%)	F 15(30.6%)	G 3(6.4%)	19
Worse	H 3(9.4%)	I 1(2.0%)	D 15(31.9%)	19
Total	32 (100%)	49 (100%) <i>P</i> < 0.01	47 (100%)	128

\* The evaluations of psychiatric and surgical status on follow-up of 128 subjects are combined in one table to show the association of one type of evaluation with the other. The vertical columns of the table show the psychiatric evaluations after convalescence (improved or continuing adjustment, persisting maladjustment, and worse adjustment). The horizontal columns contain the surgical evaluations after convalescence (improved, stationary, worse). In each block there are the number of cases and percentage of the column. The capital letters refer to a later part of the text. The equation  $P < 0.01$  is a value obtained from  $\chi^2$ , indicating that the null hypothesis may be rejected regarding an association between psychiatric status and surgical status on follow-up.

cal change suggests that there is some interaction between the psychologic and the physiologic processes during recovery from surgical illness and treatment. This interaction may have etiologic importance in determining the total outcome of convalescence.

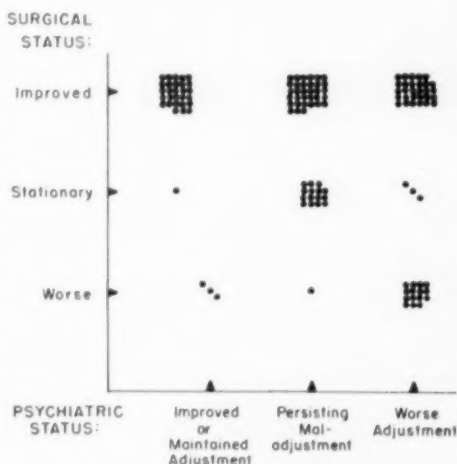


Fig. 2.—Distribution of cases according to evaluations of psychiatric and surgical status on follow-up. Each dot represents one case placed in the scattergram, as evaluations of surgical status and psychiatric status three to six months after discharge would indicate.

On closer inspection, some further trends appear in Table 2.

1. In this series of patients the majority improved surgically. The surgically improved patients fell almost equally into the three categories of psychiatric status on follow-up.

2. Most of the patients whose surgical conditions remained stationary were rated as manifesting a persistent psychiatric maladjustment three to six months after discharge.

3. The majority of the patients whose surgical condition became worse also presented a worse psychiatric adjustment on follow-up.

#### Relationship Between Degrees of Anxiety-Fear Observed During Phases of Hospital Stay and Type of Psychiatric Adjustment Observed on Follow-Up

One of the observations made on each patient consisted of an evaluation of the degree of anxiety or fear experienced during two different phases of the hospitalization, preoperative and postoperative. In agreement with other investigators,<sup>5</sup> it was felt that an attempt to distinguish between anxiety and fear in the clinical setting would be unnecessary and futile. We are of the opinion that the patient facing surgery is experiencing a compound of the two emotions; that when a person says he is "afraid" of surgery a portion of his feeling consists of anxiety, stemming from internal conflict. When the patient is tense and has no expressed feelings about the reality situation, he is describing anxiety, but his feelings may be at least partly explained by fear of an external threat, such as surgery. In both cases it is an overly complex task to tease apart such coexistent emotions.

The criteria for the presence of anxiety or fear were as follows:

1. Verbal expression of fear, tension, or anxiety from the patient
2. Physiological concomitants of anxiety, such as tachycardia, perspiration, tremor, palpitations, dryness of the mouth, and rapid or sighing respiration

3. "Bravado anxiety"—overprotestation disclaiming anxiety or fear, but manifesting the physiological concomitants of them

Nearly all of the patients who were considered anxious or fearful presented the first two criteria. However, a small minority disclaimed feelings of fear or anxiety, either spontaneously or in response to inquiry, although revealing its physiological concomitants; and when doing so they would speak with intensity and repeatedly on the subject, saying, "I'm not afraid; I'm not tense; I'm not scared." We assumed that these patients truly perceived their anxiety, since the physiological concomitants were present, but some need arising from the relationship with the interviewer required that they disclaim, in fact denounce, the idea that fear or anxiety was present.

This phenomenon must be differentiated from the mechanism of denial. In our opinion, when the defense of denial is employed, the anxiety is successfully repressed. In the case of bravado anxiety there is no repression but, rather, a form of suppression arising in the interpersonal situation between the interviewer and the subject.

When it seemed from interview or psychological testing that anxiety was present but bound in denial, in neurotic symptoms, in psychosomatic disorders, or by psychotic or quasipsychotic symptoms, the observation was recorded but not labeled as *free* anxiety or fear. When the affects of free anxiety or fear were discovered, they were rated on a four-point scale, as follows:

1. No noticeable free anxiety or fear
2. Moderate free anxiety or fear
3. Severe free anxiety or fear
4. Anxiety or fear approaching panic.

Anxiety-fear was rated independently by two team members (J. T. and H. S.), including one (J. T.) who actually interviewed subjects of the research and who was closest to the data as the material was collected. A check of reliability of the rating system was accomplished by presenting the second team member (H. S.) with the typed interview notes, other relevant data, and the criteria for judging anxiety-fear.

# SURGICAL ILLNESS—ADJUSTMENT

TABLE 3.—*Relationship Between Anxiety-Fear Occurring During Hospitalization and Type of Psychiatric Adjustment Found on Follow-Up in Patients Having Actual Operations*

A. Preoperative Anxiety-Fear and Psychiatric Status				
Anxiety-Fear Ratings	Improved or Maintained Adjustment	Persisting Maladjustment	Worse Adjustment	Total
1*	2	12	4	18
2	4	9	16	29
3 & 4	20	7	10	37
Total	26	28	30	84
Mean for group	3.0	1.8	2.2	
		$P < 0.01 \uparrow$		
B. Postoperative Anxiety-Fear and Psychiatric Status				
Anxiety-Fear Ratings	Improved or Maintained Adjustment	Persisting Maladjustment	Worse Adjustment	Total
1*	7	7	2	16
2	13	11	5	29
3 & 4	7	10	24	41
Total	27	28	31	86
Mean for group	1.5	2.1	3.0	
		$P < 0.05 \uparrow$		

\* Anxiety-fear was rated in each patient on an ascending scale, with a rating of 4 for highest degree of anxiety-fear and 1 for little or no anxiety-fear.

† The association of anxiety-fear levels and psychiatric status was significant at the 1% level in the instance tabulated in A and at the 5% level in B.

Correlations between the ratings of the independent evaluators varied between 0.4 and 0.5. Such correlations are significant at the 1% level by statistical test but do not indicate high reliability of the rating system. We suspect this low level of reliability has resulted from the fact that something has been lost between actual observation and typed protocol. The figures to be reported will be those of the rater who interviewed the patients, and thus had access to the cues (Table 3).

Patients who maintained a good adjustment or actually improved after surgery in their over-all adjustment reported high degrees of anxiety preoperatively. Those patients who were later found to have a persisting, unchanging over-all adjustment after surgery showed little or no anxiety preoperatively. However, patients who appeared to have a worse personality adjustment after surgical illness and treatment felt intermediate degrees of preoperative anxiety or fear.

In the case of postoperative anxiety or fear we found that the patients feeling almost complete relief from anxiety or fear during the interval between surgery and discharge were very likely to be improved in psychiatric status on follow-up. The patients who suffered a slight increase of anxiety or fear postoperatively were found in the postconvalescent evaluation to manifest persistent maladjustment. The patients whose personality adjustment appeared to be aggravated on follow-up had experienced a marked increase of anxiety during the days after surgery. These differences were statistically significant. The measures of anxiety before and after operation were made from observations during the hospital stay only. Evaluations of psychiatric status are based upon a comparison of observations made three to six months after discharge with those made upon initial contact with the patient.

The findings summarized in Table 3A and B apply only to those patients having a treatment procedure that could definitely be called an operation. Our experience with surgical patients has convinced us that nearly every patient on a surgical ward secretly or openly expects that he or she is to have surgery. Nearly every surgical admission and course in the hospital may be described in the same phasic fashion that the words "preoperative" and "postoperative" imply. There is the initial phase, when the person is likely to be wondering and fearful about his diagnosis and expectations for treatment. The methods of diagnosis and the nature of the treatment are mystifying. He starts the daily routine with examinations and tests. He listens intently and with various degrees of trepidation to the technical discussions of his doctors. As the day of decision nears, there is potential for increasing and culminating tension. This phase comes to a turning point when suddenly the patient hears that diagnosis is sure and/or that decisions have been made. He may hear that he needs no surgery and wonders why, or surgical treatment starts

that is not technically labeled as an operation, but, nevertheless, he wonders about the results. The turning point marks the beginning of the second phase, corresponding to the postoperative period. In this phase there is likely to be a settling and lessening of the dramatic stresses of the initial phase. The patient no longer awaits surgery but must make an adjustment to a new situation, that of adapting to treatment and of accepting a more certain degree of recovery or disability. The day of discharge is now the immediate goal toward which he strives or drifts unwillingly.

Anxiety and fear were rated for these two phases of the hospital course in a manner similar to that for the group who had operations.

In Table 4A and B are illustrated the relationships between follow-up psychiatric status and the changes in degrees of anxiety and fear for all patients on whom information was sufficient. The relationships were very similar to those demonstrated in the patients who had operation (Table 3). Fig.

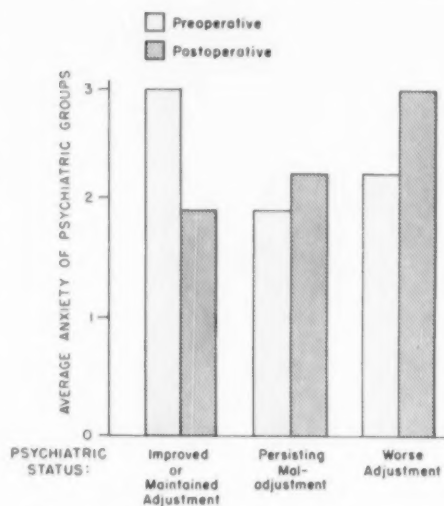


Fig. 3.—Average ratings of preoperative and postoperative anxiety of the patients in each group of follow-up psychiatric status. Patients were rated on an ascending four-point scale (see text) for levels of pre- and postoperative anxiety or fear. The same patients were evaluated psychiatrically on follow-up, and the histogram above shows the average anxiety or fear for each category of psychiatric evaluation.

TABLE 4.—Relationship of Anxiety-Fear Occurring During Hospitalization and Type of Psychiatric Adjustment Found on Follow-Up on All Patients Whether or Not an Operation Was Performed

A. Phase 1: Anxiety-Fear Equivalent to Preoperative Period Psychiatric Status				
Degrees of Phase 1 Anxiety-Fear	Improved or Maintained Adjustment	Persisting Maladjustment	Worse Adjustment	Total
1	2	19	8	29
2	5	12	19	36
3	15	16	16	47
4	8	1	2	11
Total	30	48	45	123
Mean for group	3.0	1.9	2.2	
		$P < 0.01 *$		

B. Phase 2: Anxiety-Fear Equivalent to the Postoperative Period Psychiatric Status				
Degrees of Phase 2 Anxiety-Fear	Improved or Maintained Adjustment	Persisting Maladjustment	Worse Adjustment	Total
1	8	11	2	21
2	15	15	9	39
3	7	18	22	47
4	0	2	14	16
Total	30	46	47	123
Mean for group	1.9	2.2	3.0	
		$P < 0.01 *$		

\* The association of anxiety-fear levels and psychiatric status is significant at the 1% level in both cases.

ure 3 graphs the changes in anxiety level from one phase of hospital course to another in the various psychiatric groups.

The anxiety-fear patterns during the preoperative (or Phase 1) and postoperative (or Phase 2) periods may be summarized as follows:

1. Patients who had high degrees of anxiety-fear in the early, or preoperative, phase of the hospital course improved or maintained a good psychiatric adjustment. In the second, or postoperative, phase these patients were relatively free of anxiety-fear.

2. Patients who had a low plateau of anxiety level in both phases remained stationary in their maladjustment.

3. The patients who suffered a rise from intermediate degrees of anxiety-fear in the early phase to a higher level in the later, or postoperative, phase were found to be worse in their over-all adjustment on follow-up. These differences are statistically significant.

### Relationship of Some Personality Features and Patterns of Response to Surgical Illness and Treatment

We discussed in seminars during our research the association of individual modes of adapting psychologically with the types of response to illness and surgical treatment. We examined our findings for the existence of possible correlations between types of personality integration and the physiology of recovery from illness and surgery. If formulations of the psychophysiology of recovery from surgical illness are valid, they would have practical clinical significance in that the surgeon or psychiatric consultant would have some new bases for expectations for the ways in which individual patients will manage convalescence and recovery. A greater knowledge of the interaction of psychological and physiological forces would assist in predicting the outcome of the process of convalescence.

In Table 2 there are five groups of numerical significance, labeled A, B, C, D, and E. As demonstrated in an earlier section, these groups differ with respect to combined evaluations of psychiatric and surgical status at the time of follow-up.

If we set up an hypothesis which states that psychodynamic patterns or modes of personality integration are significantly associated with the physiological events of illness, treatment, and convalescence and with the simultaneous changes in personality adjustment, we could support or refute the hypothesis by answering two questions:

1. Do the members of each Group A, B, etc. (categories of psychiatric-surgical change), share common psychological problems and a characteristic manner of adapting?

2. Do these shared aspects of personality distinguish each group from the other groups?

It appears from our analysis of the interview data, psychological tests, social case work findings, and all available evidence that both questions may be answered in the affirmative. We are led to believe that the hypothesis of an association, and thus possibly an etiologic interaction, between personality adaptational patterns and the

psychiatric and surgical outcome of surgical treatment has basis in our findings.

Following is a summary of our evaluations of each group:

#### GROUP A: *Improved surgically—improved or maintained adjustment*

Members of this group were dealing actively, if neurotically, with the problems and difficulties of fulfilling masculine or feminine roles, including sexual feeling and behavior. These efforts led most frequently to excessive passivity or hyperaggressive behavior in men and to masochistic problem-solving behavior in women. The tendency of these patients to manifest high degrees of preoperative anxiety, declining after operation, was found to be in company with psychological flexibility or a capacity to vary and remobilize defenses to meet new stress.

#### GROUP B: *Improved surgically—persisting maladjustment*

These people appeared to require rigid and incapacitating psychological defense mechanisms. They were coping with unresolved and ungratified dependency needs, and the hostility consequent to these needs was managed by techniques of suppression, reaction formation, and occasional acting out. Their personalities were most frequently featured by an apathetic, anhedonic, and monotonous quality.

#### GROUP C: *Improved surgically—worse adjustment*

This group included patients who resembled Group A in flexible reactivity, but whose emotional conflicts appeared more profound and less manageable, resulting after convalescence in a high incidence of depression and other neurotic symptoms. The patients suffered high anxiety preoperatively, and, in contrast to Group A, this affect in most did not decline in intensity after operation.

#### GROUP D: *Worse surgically—worse adjustment*

The patients differ from Group C mainly in degree of intensity of emotional conflict. Deep-going hostility-guilt conflicts arising from frustration of inordinate urges to be

taken care of and supported led to severe neurotic and psychotic depressive reactions in many cases in this group.

*GROUP E: Stationary surgically—persisting maladjustment*

This group was featured most by rigidity of psychological defense mechanisms and primitive methods of coping with problems, and the patients had the most chronic neurotic adaptations. These persons most resembled Group B but differed in that there was even greater lack of resiliency and in that adjustment was almost totally organized at the level of survival, requiring a fixed defense system to protect against further deprivation. In every case the surgical illness was of extremely long duration, without change, and appeared to have a necessary function in the patient's mode of adjustment.

A comparison of psychological themes that appear to distinguish these five groups demonstrates the potential for significant interactions between emotional adjustment and the effectiveness of recovery from surgical illness. The two groups of surgically improved patients—those who improved in psychological adjustment and the group that became psychologically worse—were both characterized by flexibility and reactivity of character, though the "worse" group had deeper, severer conflicts. The third category of surgically improved patients, those with persisting maladjustment, differed from the first two in showing less reactivity, a less varied repertoire of techniques of adjustment to stress, and a tendency to have severe problems in the area of dependency. Conflicts of frustrated dependency, hostility-guilt, and depression featured the group that was found to be worse both surgically and psychiatrically. These patients showed trends toward inhibition of overt expression of emotions and somatic reactions in response to emotional stress. Finally, the patients whose maladjustment persisted while their surgical condition remained stationary were the least integrated and mature, most fixed, and had the most obstinate

TABLE 5.—*Evaluation of Psychiatric and Surgical Condition After Convalescence*

	Flexible Character Structure	Rigid Character Structure
Severest conflicts	Group C Improved surgically and worse adjustment	Group E Stationary surgically and persisting maladjustment
Less severe conflicts	Group A Improved surgically and improved adjustment	Group B Improved surgically and persisting maladjustment

psychological problems. The patients in the last two groups with chronic stationary conditions showed the strongest trends toward expressing psychological conflicts through somatic preoccupation.

A paradigm (Table 5) illustrates on two axes, intensity of emotional conflict and flexibility of problem-solving techniques, the pattern of differences among four groups of our patients evaluated simultaneously with regard to psychiatric and surgical condition after convalescence.

The groups differed in their ability to prepare for and cope with emotional stress or impending physical injury. The availability of psychological resources or maneuverability and resiliency of techniques of adaptation may best account for the varieties of postconvalescent adjustment. Our data indicate that flexible adjustment capacities are most frequently associated with a psychological resiliency that permits a strong recovery from surgical illness. On the other hand, exhausted and inflexible psychological adaptability is most frequently associated with stationary, unrecovered surgical conditions. Which of these variables is cause and which is effect is a question not answered in our research. Both sets of variables may simply be manifestations of another complex of etiologic factors that we did not encounter in our study. We would endorse a multiple factor theory of etiology as the most comprehensive explanation for the relationships we have described, with a different composition of etiologic factors for each person. We are inclined to account for the associations of psychological and somatic consequences of surgical



illness by the use of a metaphor. When military units are worn out or are entirely mobilized and dug in against prolonged siege on a single front, there are none that can be rallied to deal with a new attack from another direction. When adaptive resources are wholly organized to defend against physiological stress, there may be little strength to meet psychological threat. In parallel fashion, physiological adaptation may be less effective when psychological resources are entirely mobilized against stress.

### Shifts in Psychological Balance or Patterns of Adjustment After Surgery

After consideration of the personality changes in surgical patients in one dimension, a vertical one, toward improvement, aggravation, or stasis, it becomes apparent that there is another continuum upon which change can be projected—a horizontal scale that may or may not be associated with improvement or the reverse. It is conceivable that any stress could result in changes in patterns of behavior, in choice of psychological defense or symptom, or in the characteristic mode of adaptation without such alterations representing a movement toward improvement or aggravation of adjustment. For example, a person who had adapted to inner self-doubt by means of anxious virility and ostentatious foolhardiness, and who then overreached himself and sustained a head injury, was found later to have relinquished his old habits of high-speed driving, fighting, drinking, and sexual promiscuity and to have become inactive, impotent, and recurrently stricken with the symptoms of anxiety. In such a case the balance shifted, and the defenses against, or means of coping with, anxiety were drastically redeployed. Conceptually, this shift of adjustment patterns could be considered "better" or "worse" or neither. This horizontal change in reaction pattern was frequent in our series, often occurring simultaneously with vertical change. The commonest of these shifts were as follows:

	% of Total ‡
1. Neurotic symptoms replacing somatic symptoms	14.1
2. Somatic symptoms replacing neurotic symptoms §	10.2
3. Neurotic symptoms replacing behavior disorder	14.1
4. Behavior disorder replacing neurotic symptoms	4.7

The patients who became worse psychiatrically and improved surgically (Group C) included the highest percentage of these alterations in patterns of adjustment. This association of Group C with the horizontal change in adaptation is statistically significant ( $P < 0.01$ ). Equally predominant among the types of change in the Group C patients were (1) neurotic symptoms replacing medical or surgical complaints, and (3) neurotic symptoms replacing signs of a character and behavior disorder.

TABLE 6.—Frequency of Change in Adjustment Patterns Occurring After Surgery in Various Groups of Patients

Group	Percentage of Group Changing
C Improved surgically, worse adjustment	78.6
D Worse surgically, worse adjustment	40.6
A Improved surgically, improved adjustment	13.8
B Improved surgically, persisting maladjustment	
E Stationary surgically, persisting maladjustment	

Two of the commonest shifts in type of adjustment are illustrated by the following examples:

#### 1. Neurotic symptoms replacing somatic symptoms

A 34-year-old Negro woman had suffered menometrorrhagia and very severe dysmenorrhea for several years and for a decade had been in a pleasureless, unstable marriage, marked frequently by bickering and nearly as often by the recurrent deserts of an alcoholic husband. During this time neurotic symptoms had not been notable. A fibroid uterus was diagnosed and a hysterectomy elected, which was performed without ensuing major surgical complications. Symptoms of an

‡ Total—128 cases on which information was sufficient.

§ In this section "somatic symptoms" refers to all bodily complaints whether or not a structural basis could be demonstrated.

agitated depression made an appearance post-operatively, and on follow-up the patient was suffering nearly overwhelming anxiety, dissociative episodes, and a delusion of persecution. Guilt and fear of harm over the emergence of powerful sexual drives were found to be underlying the anxiety, with resultant neurotic and quasipsychotic symptoms.

## 2. *Neurotic symptoms replacing behavior disorder*

A 40-year-old white laborer who had managed a marginal socioeconomic adjustment, supporting his family at the bare subsistence level while venting whatever rebellion he felt in weekend drinking and brawling, fell 25 ft. from the end of a teetering scaffold. He was admitted for observation of a possible fracture of cervical vertebrae and discharged three days later after careful x-ray examination showed no vertebral injury. He spoke timidly during the hospital stay of his suspicion that someone had carelessly constructed the scaffold. Soon thereafter the patient began to experience attacks of trembling, perspiration, and palpitation. He had severe headaches, a startle reaction, and frequent nightmares, which continued until follow-up. He complained bitterly, though vaguely, of neck pain, had not sought employment, and was planning a suit for compensation. It seemed clear that whether or not he was successful in his suit he would not soon be restored to a position of supporting his family.

## Comment

Though we feel that it is useful conceptually to consider personality change as having two axes, one horizontal and the other vertical, and we feel that we have observed both in our series, still it must be noted from figures on the association of the types of change that the usual case alters with respect to shifts in adaptation and toward improvement or aggravation of adjustment.

Two clues helpful in selecting the cases needful of psychotherapy on surgical wards may be developed from this consideration of shifts in patterns of defenses against anxiety.

First, we have observed that those patients who manifested anxiety and/or depression shortly after the surgery were found likely to develop psychiatric difficulty in the postconvalescent period. The patients who became worse psychiatrically

most frequently manifested shifts in balance of defenses. In addition, we have the impression that enhanced feelings of guilt are underlying the postoperative anxiety. This increase in guilt anxiety appears to have arisen from the stimulation of hostile or sexual impulses in the surgical experience, or previously latent guilt has been confirmed in a fantasy of surgery as punishment. When patients are found postoperatively to be suffering increased guilt anxiety and show shifting patterns of adaptation, they should be considered for psychotherapy to prevent a worse psychiatric adjustment following convalescence.

Secondly, patients who express themselves by pathological acting out and then suffer either coincidentally or by unconscious design a traumatic injury to some part of the body should be considered for psychotherapy. Their shift in mode of psychological integration is toward symptomatic neuroses, usually anxiety reactions. In our opinion, many persons in the latter category are more suitable candidates for psychotherapy in this post-traumatic and anxiety-heightened time of their lives than they ever have been or ever will be again. These criteria for psychiatric referral do not include all patients who need treatment, nor would all patients who manifest them be suitable candidates. These clues may bring the psychiatric consultant two steps closer to a formulation of the problem.

Other researchers have dealt with observations on individual alterations in methods of adaptation as a reaction to surgery. Kaplan<sup>6</sup> has shown the effect upon the personality of integration of chronic cardiac patients undergoing mitral commissurotomy, a procedure that converts a person from invalidism to activity. Browning and Houseworth<sup>7</sup> present a series of patients who had a gastrectomy for treatment of a peptic ulcer. Such patients showed a high incidence of neurotic symptoms, character change, or new psychosomatic illness after operation. In the latter work, the authors interpreted their findings to indicate that

when a person is deprived of an organ previously used as a channel for expression, his conflicts will emerge elsewhere. Our findings suggest that the situation is more complex, that the stress of the experience and many other factors may force an alteration in type of personality integration.

Though the limitations of our research do not allow more than a simple reporting of the phenomena of change, observations made with surgical patients of alteration in the patterns and balance of defenses open an area for later study. It is interesting to ask whether there are other like experiences capable of the same effect. How often does the vigorous and menacing neurotically aggressive character become a trepidating phobic, and what are the situations that result in such metamorphoses? What circumstances lead one from relief of bodily symptoms to increased neurotic complaints or the reverse? In what social context does either change occur? Psychotherapy often accomplishes such turnabout alterations, as does religious experience and the reaction to widespread and pervasive socioeconomic revolution. Our observation of the natural history of the surgical experience and the changes in personality occurring during and after it has led us to the conclusion that surgery is comparable to some of these other forces in modern society in its potential for profound effect upon psychological adaptation.

### Summary and Conclusions

The over-all adaptation to surgical illness and treatment has been studied in a series of 200 randomly selected surgical patients by means of observations during hospitalization, convalescence, and recovery by a multidisciplinary team of investigators.

Approximately 70% of the patients were rated as improved surgically three to six months after discharge from the hospital. However, these same patients were found to be divided equally with respect to change in psychiatric status three to six months after discharge from the hospital. Among

the surgically improved patients, about one-third were improved, one-third manifested persisting maladjustment, and another third was worse in adjustment. The surgically stationary patients were almost all rated as persisting in maladjustment, while the surgically worse were also worse psychiatrically after the convalescent interval.

A correlation between postconvalescent psychiatric adjustment and the levels of anxiety and/or fear experienced just before and soon after surgical treatment was demonstrated. Increased anxiety and/or fear appearing preoperatively were associated with the maintenance of a good or an improved personality adjustment. The same affects appearing postoperatively were associated with a worse adjustment after convalescence. Patients who had personality maladjustments that persisted showed little anxiety or fear in either the preoperative or the postoperative phase of hospitalization.

Our studies of the relationship of modes of personality adaptation to the course of the surgical experience indicate that flexible adjustment capacities are most frequently associated with a physiological resiliency that permits a strong recovery from surgical illness. On the other hand, exhausted and inflexible psychological adaptability is most frequently associated with stationary, unrecovered surgical conditions. Which of these variables is cause and which is effect is a question not answerable in this study.

Shifts in the balance or pattern of personality integration were shown to occur after the surgical experience. These shifts were as follows: (a) neurotic symptoms replacing somatic symptoms; (b) somatic symptoms replacing neurotic symptoms; (c) neurotic symptoms replacing behavior disorders, and (d) behavior disorders replacing neurotic symptoms.

The group of patients who became worse psychiatrically and improved surgically experienced the highest percentage of shifts in adjustment patterns from somatic symptoms to behavior disorders or to neurotic symptoms. The same group was most liable

to an increase in guilt anxiety, which in most instances appeared to have origins in the stimulation of hostile or sexual impulses by experience with surgery or from conceiving of surgery as a punishment.

We have the impression that when guilt, anxiety, or depression is on the rise in the immediate postoperative period, such a reaction may forewarn the attending physician of the development of psychiatric difficulties following convalescence. Preventive psychotherapy should seriously be considered when feasible to avoid chronic maladjustment.

Also, those persons who customarily express inner conflicts by aggressive, ostentatious, and foolhardy acting out, and then suffer a traumatic injury, are more suitable and available candidates for psychotherapy in this post-traumatic period of their lives than at any other time. Without intervention they developed in our observations disabling neurotic or somatic symptoms.

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# The Face-Hand Test in Schizophrenic Children

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It has been postulated that childhood schizophrenia represents an alteration of the central nervous system.<sup>1-5,16</sup> Thus, Lauretta Bender has declared that "the schizophrenic child reveals pathology at every level and in every field of integration within the function of the central nervous system, be this vegetative, motor, perceptive, intellectual, emotional or social. . . . It must be conceived of as striking at the substratum of all integrative functioning."<sup>19</sup>

In clinical practice, the schizophrenic child's defect in central integration is seldom demonstrable on standard neurological and electroencephalographic examination. Special techniques, e. g., studies of postural reflexes and visual-motor coordination, are needed to elicit neurological defects. A recent addition to this repertoire of special procedures has been M. B. Bender's face-hand test.<sup>9,13</sup> In a series of studies Bender and his associates<sup>9,7,11,18</sup> have shown this task to have clinical value as a diagnostic test of diffuse cerebral dysfunction. The face-hand test consists of touching the subject, whose eyes are closed, simultaneously

on the cheek and the dorsum of the hand for at least 10 trials. In contrast to normal adults, who may make errors only on the initial trials, brain-damaged patients with severe mental changes ("organic mental syndrome") make persistent errors beyond 10 trials. When errors are made, they occur in the recognition of the hand stimulus, whereas the cheek stimulus is almost always correctly reported. The errors in the recognition of the hand stimulus are of two types: (1) extinction, i. e., failure to report the stimulus, and (2) displacement or mislocalization of the hand stimulus to another part of the body, usually the other cheek. In patients with severe alterations of brain function the hand stimulus is sometimes displaced into extrapersonal space (exosomesthesia).<sup>18</sup>

Bender and Fink<sup>7</sup> have found the face-hand test useful in differentiating adult schizophrenic hospital patients from those with behavioral changes due to massive brain lesions. In contrast to patients with "organic psychoses," adult schizophrenics do not make persistent errors. Their perceptual pattern is similar to that of normal adults.

Fink and Bender<sup>10</sup> have shown that young children make the same kind of errors in cutaneous perception as do adults with altered brain function. Below the age of 6 years normal children have a positive face-hand test; i. e., they failed to identify both stimulus correctly within 10 trials. The children are "face-dominant" in that they report the face stimulus but not the hand stimulus. Younger children fail to perceive the hand stimulus even when tested with the eyes open. However, by the age of three years simultaneous stimulations of symmetric body areas, e. g., both cheeks and both hands, are correctly identified.

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The face-hand test is related to mental age in mentally defective<sup>12</sup> as well as in normal children. In mentally defective adults there is a high correlation between performance on the Stanford-Binet and the face-hand test. In general, defectives whose mental ages are below 7 years are positive; those with mental ages above 7 years are negative. As a result, Fink, Green, and Bender<sup>12</sup> feel that performance on the face-hand test is a valid indication of mental age above and below 7 years. Studying over 200 normal and brain-damaged children, Cohn<sup>8,9</sup> has confirmed the findings of Fink, Green, and Bender. Cohn states that "a persistence of . . . rostral [face] dominance in a well-developed child past the age of six years has proved to be fair evidence of mental retardation."<sup>26</sup>

The face-hand test would appear to be an excellent tool for the evaluation of the integrative level of severely disturbed children. It is simple and brief; it can be administered as a nonverbal test in which the child points to the area touched.

Specifically, this investigation was concerned with the following problems:

1. Does the pattern of perception of schizophrenic children differ from that of normals?
2. Do children diagnosed as nonschizophrenic behavior disorders differ from schizophrenic children?
3. What is the relation of mental age, as measured by the Stanford-Binet scale, to performance on the face-hand test in these abnormal children?

### Subjects

The experimental group consisted of 18 schizophrenic children in residential treatment, whose ages ranged from 7 years 2 months to 9 years 1 month. A clinical control group was composed of 9 children, living in the same residential treatment center, whose diagnoses fell into a variety of nonschizophrenic behavior disorders. The latter group ranged in age from 6 years 7 months to 9 years. Ninety-four public school children, ranging in age from 5 years 6 months to 8 years 11 months, served as nonclinical controls. No attempt was made

to screen out these children for any reason. The public school group included some children with behavior problems, as well as a few with subnormal intelligence.

### Procedure

The face-hand test consisted of 10 trials of asymmetric stimuli, face and hand (six contralateral and four ipsilateral), and four trials of symmetric stimuli (two face-face and two hand-hand). The order of stimulation is given in Table 1. (This procedure was slightly different

TABLE 1.—*Presentation of Face and Hand Stimuli*

1. Right cheek-left hand
2. Left cheek-right hand
3. Right cheek-right hand
4. Left cheek-left hand
5. Right cheek-left cheek
6. Right hand-left hand
7. Right cheek-left hand
8. Left cheek-right hand
9. Right cheek-right hand
10. Left cheek-left hand
11. Right cheek-left cheek
12. Right hand-left hand
13. Right cheek-left hand
14. Left cheek-right hand

from that employed by Fink, Green, and Bender.<sup>12</sup>) Each child was tested first with the eyes closed and then with the eyes open. The test was classified as positive if the child failed consistently to identify both stimuli within 10 trials. The test was negative if the child learned to identify both stimuli within 10 trials and thereafter. Occasionally a child gave an erratic performance, succeeding on one or two trials but failing on others. In such a case the testing was continued beyond the usual 10 face-hand trials in order to be certain of classification. The number of errors made by each child during the 10 asymmetric and 4 symmetric trials was recorded.

Each child was tested individually. The child sat with his hands on his knees facing the examiner. The instructions were as follows: "I am going to touch you. Point to where I have touched you." If after the second trial the child pointed to only one place, he was asked if he had been touched in any other place. The children in residential treatment were retested within a month after the initial examination. The public school group was not retested. All children in residential treatment had been previously tested with the Stanford-Binet intelligence test.

### Results

*Perceptual Errors.*—Both normal and abnormal children made essentially the same



## FACE-HAND TEST IN SCHIZOPHRENIC CHILDREN

TABLE 2.—*The Face-Hand Test in Public School Children*

Age Group	N	Mean Age, Yr.	Eyes Closed		Mean No. Errors	Eyes Open		Mean No. Errors
			Pos.	Neg.		Pos.	Neg.	
5 yr. 6 mo.-5 yr. 11 mo.	13	5.9	6	7	6.2	3	10	3.1
6 yr. 0 mo.-6 yr. 11 mo.	29	6.4	12	17	6.6	5	24	3.0
7 yr. 0 mo.-7 yr. 11 mo.	25	7.6	1	24	3.3	0	25	0.5
8 yr. 0 mo.-8 yr. 11 mo.	27	8.5	2	25	2.2	0	27	0.5

kind of errors. Errors were rarely made on simultaneous symmetric stimulation of both cheeks or both hands. On stimulation of the cheek and hand, the cheek was almost always correctly identified. The errors made were in the perception of the hand stimulus. The most frequent type of error was hand "extinction." Displacement of the hand stimulus to the opposite cheek was common, particularly among the schizophrenic children. One schizophrenic child displaced the stimulus into extrapersonal space (exosomesthesia). Since errors were rarely made on simultaneous stimulation of both cheeks or both hands, the quantitative analysis of the data was restricted to the 10 face-hand trials.

*Public School Children.*—The results for the public school children are summarized in Table 2. The most striking finding is the decrement in the number of positive performances between the 6- and the 7-year-old groups. When tested with the eyes closed, the 5½-year-old group was similar to the 6-year-old group: 46% of the 5½-year-old group, as compared with 41% of the 6-year-old group, were positive. However, only 3 out of 52, or 6%, of the children 7 years of age or older were positive. The mean number of errors made by each age group also showed a marked drop. The 5- and 6-year-old groups made twice as many errors as the 7-year-old groups. Thus, the average 7-year-old child learned to perceive both face and hand stimuli by the fourth

trial. Identification of the hand stimulus on face-hand stimulation frequently followed immediately after the symmetric trials. It would appear that bilateral stimulation served as a clue to perceptual learning of asymmetric touches. As was expected, fewer errors were made in each group when tested with the eyes open. No child 7 years of age or older had a positive test with the eyes open. There were, however, marked individual differences in performance within each age group. A few of the 5- and 6-year-old children made errors only on the first or second trial, whereas some of the 7- or 8-year-olds made many errors.

*Comparison of Schizophrenic and Public School Groups.*—In contrast to the public school children, all of whom were cooperative, two of the schizophrenic children were nontestable. These two were autistic, noncommunicating children, who did not appear to understand the instructions. There was some difficulty in maintaining the attention of a few of the more disturbed schizophrenic children throughout the test, even though it took less than 10 minutes to administer.

The group data are presented in Table 3. Of the 16 schizophrenic children tested, 13 were positive with the eyes open or closed. When compared with a control group consisting of 7- and 8-year-old public school children, the schizophrenic group was significantly different from the public school group at the 0.001 level (Table 4).

TABLE 3.—*The Face-Hand Test in Schizophrenic Children*

Age Group	N	Mean Age, Yr.	Eyes Closed		Mean No. Errors	Eyes Open		Mean No. Errors
			Pos.	Neg.		Pos.	Neg.	
7 yr. 2 mo.-7 yr. 11 mo.	10	7.6	8	2	8.8	8	2	7.7
8 yr. 0 mo.-8 yr. 11 mo.	5	8.5	4	1	9.0	4	1	9.0
9 yr. 0 mo.-9 yr. 11 mo.	1	9.1	1	0	10.0	1	0	10.0

TABLE 4.—Comparison of Face-Hand Test Performances of Public School and Schizophrenic Children

Group	N	Mean Age, Yr.	Eyes Closed				Eyes Open			
			Pos.	Neg.	$\chi^2$ <sup>a</sup>	P	Pos.	Neg.	$\chi^2$ <sup>a</sup>	P
Public school	52	8-0	3	49	39.02	0.001	0	52	48.21	0.001
Schizophrenics	16	7-11	13	3			13	3		

<sup>a</sup> Corrected for discontinuity.

Aside from the higher frequency of positive performance in the schizophrenic group, there were two other major differences between the normals and the schizophrenics. In the normal group, children 7 years old or more made few errors when tested with the eyes open. Yet in the schizophrenic group children made almost as many errors with the eyes open as closed. In the normal group errors decreased with age (Table 2). However, in the schizophrenic group there was no relation between chron-

ceeded in identifying both face and hand stimuli. On the other hand, the schizophrenic children who were positive consistently failed to identify the hand stimulus.

A comparison of the nonschizophrenic behavior disorder group and the public school controls is shown in Table 6. In contrast to the schizophrenic group, the behavior disorder group did not differ significantly from the controls when tested with eyes closed. They did, however, differ at the 0.02 level of significance when tested with eyes open.

TABLE 5.—The Face-Hand Test in Nonschizophrenic Behavior Disorders

Age Group	N	Mean Age, Yr.	Eyes Closed			Eyes Open		
			Pos.	Neg.	Mean No. Errors	Pos.	Neg.	Mean No. Errors
6 yr. 7 mo.	1	6-7	0	1	7.0	0	1	7.0
7 yr. 7 mo.-7 yr. 11 mo.	2	7-10	0	2	2.3	0	3	0.0
8 yr. 2 mo.-8 yr. 5 mo.	4	8-4	2	2	5.7	2	2	3.7
9 yr. 0 mo.	1	9-0	0	1	1.0	0	1	0.0

ological age and face-hand test performance. This may have been due, in part, to the small sample of schizophrenic children.

*Comparison of Nonschizophrenic Behavior Disorder and Public School Groups.*—The results for the nonschizophrenic behavior disorder group are presented in Table 5. The behavior of this group was different from that of the schizophrenic children. They were cooperative and testable. Only two children in this group were positive. These two children with positive face-hand test performances were different from the schizophrenics in that they occasionally suc-

ceeded in identifying both face and hand stimuli. However, it should be noted that this difference was based on only two positive cases.

*Comparison of Schizophrenic and Nonschizophrenic Behavior Disorder Groups.*—As was pointed out previously, the behavior disorder group made fewer errors than the schizophrenic group. A comparison of the number of positive performances within each of the groups on initial testing is shown in Table 7A. Although the mean ages of the groups were almost identical, the frequency of positive performance within the schizophrenic group was significantly higher than in the behavior disorder group.

TABLE 6.—Comparison of Face-Hand Test Performances of Public School and Behavior Disorder Children

Group	N	Mean Age, Yr.	Eyes Closed				Eyes Open			
			Pos.	Neg.	$\chi^2$ <sup>a</sup>	P	Pos.	Neg.	$\chi^2$ <sup>a</sup>	P
Public school	52	8-0	3	49	0.53	0.50	0	52	5.85	0.02
Behavior disorder	9	7-11	2	7			2	7		

<sup>a</sup> Corrected for discontinuity.

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TABLE 7A.—Comparison of Face-Hand Test Performances of Schizophrenic and Nonschizophrenic Behavior Disorders on Initial Testing

Group	N	Mean Age, Yr.	Eyes Closed				Eyes Open			
			Pos.	Neg.	$\chi^2$ *	P	Pos.	Neg.	$\chi^2$ *	P
Schizophrenics	16	7-11	13	3	6.06	0.02	13	3	6.06	0.02
Behavior disorders	9	8-0	2	7			2	7		

\* Corrected for discontinuity.

*Retesting.*—The two positive cases in the behavior disorder group, as well as three children in the schizophrenic group, became negative on retest examination. Thus, only schizophrenic children remained positive on retesting. As is seen in Table 7B, there were no positive cases left in the behavior disorder group, whereas 9 out of 15 children in the schizophrenic group remained positive. The difference between the schizophrenic and the nonschizophrenic behavior

children. They were the most autistic, inattentive children in the group. These children were also intellectually retarded. Their test ages on the Stanford-Binet Scale were several years below their chronological age.

*Relation of Face-Hand Test to Mental Age.*—Performance on the face-hand test, chronological age, mental age, and IQ for each child in the schizophrenic and nonschizophrenic behavior disorder groups is given in Tables 8A and 8B. With one

TABLE 7B.—Comparison of Face-Hand Test Performance of Children with Schizophrenic and Nonschizophrenic Behavior Disorders of Retesting

Group	N	Eyes Closed				Eyes Open			
		Pos.	Neg.	$\chi^2$ *	P	Pos.	Neg.	$\chi^2$ *	P
Schizophrenics	15	9	6	26.01	0.001	9	6	26.01	0.001
Behavior disorders	9	0	9			0	9		

\* Corrected for discontinuity.

groups is significant at the 0.001 level. The retest acted as a filter in which only the least integrated children failed to learn to identify both face and hand stimuli after 20 trials with eyes closed and 20 trials with eyes open. These children were clinically distinct from the rest of the schizophrenic

exception (Case 9) all children were tested with the Stanford-Binet Form L.

The majority of children with positive face-hand performances on initial testing had IQ's below 80. The few children who had normal IQ's and were positive on initial testing became negative on retesting. The

TABLE 8A.—Individual Performances of the Schizophrenic Children on the Face-Hand Test

Case	Sex	C.A.	IQ	M.A.	Initial Test				Retest			
					Eyes Closed		Eyes Open		Eyes Closed		Eyes Open	
					Errors	Rating*	Errors	Rating*	Errors	Rating*	Errors	Rating*
1	F	7-2	69	4-11	10	+	10	+	10	+	10	+
2	M	7-4	62	4-7	9	+	10	+	9	+	7	+
3	F	7-5	71	5-3	10	+	9	+	10	+	10	+
4	M	7-5	88	6-6	8	—	0	—	0	—	0	—
5	M	7-7	80	6-1	10	+	10	+	10	+	10	+
6	M	7-7	100	7-7	7	+	7	+	0	—	0	—
7	M	7-9	71	5-6	10	+	10	+	10	+	10	+
8	M	7-9	81	6-3	10	+	10	+	8	—	0	—
9	M	7-9	92	7-2	4	—	1	—	0	—	0	—
10	F	7-9	N.T.	N.T.	10	+	10	+	N.T.	N.T.	N.T.	N.T.
11	F	8-0	57	4-7	10	+	10	+	10	+	10	+
12	F	8-1	69	5-7	10	+	10	+	10	+	10	+
13	M	8-4	80	6-8	10	+	10	+	3	—	4	—
14	M	8-8	110	9-5	0	—	0	—	1	—	1	—
15	M	8-11	45	4-0	10	+	10	+	10	+	10	+
16	M	9-1	52	4-9	10	+	10	+	9	+	10	+
Mean		7-11	75.1	5-10	8.6		7.9		6.2		5.8	

\* + indicates positive performance; — indicates negative performance.

TABLE 8B.—*Individual Performance of the Nonschizophrenic Behavior Disorder Children on the Face-Hand Test*

Case	Sex	C.A.	IQ	M.A.	Initial Test				Retest			
					Eyes Closed		Eyes Open		Eyes Closed		Eyes Open	
					Errors	Rating *	Errors	Rating	Errors	Rating	Errors	Rating
17	M	6-7	105	6-11	7	—	2	—	1	—	0	—
18	F	7-7	94	7-2	0	—	0	—	1	—	0	—
19	M	7-10	85	6-8	2	—	0	—	0	—	0	—
20	F	7-11	103	8-2	5	—	0	—	0	—	0	—
21	F	8-2	100	8-2	2	—	0	—	0	—	0	—
22	M	8-3	80	6-7	8	+	7	+	0	—	0	—
23	M	8-4	99	8-3	8	+	8	+	3	—	0	—
24	F	8-5	74	6-3	0	—	0	—	0	—	0	—
25	M	9-0	105	9-5	1	—	0	—	0	—	0	—
Mean		8-0	93.9	7-5	3.7		1.9		0.5		0	

\* + Indicates positive performance; — indicates negative performance.

children who remained positive on retesting, with one exception, had IQ's of 71 or lower. The IQ of this child was 81.

In correlating mental age with performance on the face-hand test, all children in residential treatment were combined into one group (Table 9). There was little difference between mean chronological ages of the children who were positive on the face-hand test and those who were negative. However, on the initial test, the mean mental age of the positive group was 1 year 10 months lower than that of the negative group. The biserial correlation of mental age and face-hand test performance for the initial test was  $+0.77 \pm 0.18$ . On retesting there was an even greater divergence between the mean mental age of the positive and that of the negative group. This was due to the fact that the children with the higher IQ's became negative on retesting. Indeed, the distributions of mental age scores for these two groups did not overlap at all. In other words, the mental ages in the positive group ranged from 4-11 to 6-11, as compared with 6-3 to 9-5 in the negative group. Thus, in the retesting a

perfect correlation coefficient of  $+1.0 (-0.08)$  was obtained between the face-hand test and mental age. This unique correlation undoubtedly reflects in a measure the smallness of the sample.

Some of the children of low mental age who remained positive on retesting have been studied periodically for two years. Even though they have been tested on hundreds of trials, they have as yet failed to identify both stimuli correctly. One boy in this group (Case 15, Table 8A) with an IQ of 45, is now  $10\frac{1}{2}$  years old. He mislocalizes the hand stimulus to the other cheek even when tested with his eyes open and his hands held in front of his eyes. When his hand is stimulated with a noxious stimulus (pinch, pinprick) and his cheek is simultaneously stimulated with a mild stimulus (touch), this boy will point to both places correctly. However, on subsequent trials, when retested with the usual finger touches to the hand and cheek, he again points only to the cheek and displaces the hand stimulus. In all the numerous trials he has never made errors on symmetric stimulation of both cheeks or both hands.

### Comment

The results of this study corroborate previous reports<sup>8,10</sup> which indicate that by the age of 7 years almost all normal children learn to identify simultaneously applied touches to the cheek and the hand within 10 trials. In contrast to a group of normals and institutionalized children with non-schizophrenic behavior disorders, a majority

TABLE 9.—*Correlation of Face-Hand Test with Mental Age in Combined Group of Children with Schizophrenic and Nonschizophrenic Behavior Disorders*

	Initial Test		Retest	
	Pos.	Neg.	Pos.	Neg.
N	14	10	9	15
C.A. (mean)	8-0	7-11	7-11	8-0
M.A. (mean)	5-8	7-6	5-0	7-4
Biserial <i>r</i>	$0.77 \pm 0.18$		$1.00 (-0.08)$	

of a group of institutionalized schizophrenic children failed to perceive both stimuli after 40 trials.

The schizophrenic group was not homogeneous with respect to the face-hand test. The performances of a few of the children in this group were indistinguishable from normal children in that they learned to identify both face and hand stimuli within the initial 10 trials. The schizophrenic children who were unable to perceive both stimuli showed a consistent pattern of perception identical with that seen in young children (less than 6 years) and patients with severe mental changes due to altered brain function.

Simultaneous stimuli to symmetric body areas, both cheeks or both hands, were always perceived. On simultaneous stimulation of face and hand, the face was correctly identified, whereas the hand was frequently displaced to the opposite cheek. This phenomenon has been reported in a previous study of double simultaneous stimulation in preschool schizophrenic children.<sup>17</sup> Jaffe and Bender state that "symmetry is an organizing factor in the displacement phenomena seen on bilateral simultaneous cutaneous stimulation."<sup>21</sup> Jaffe and Bender<sup>14</sup> and Korin and Fink<sup>15</sup> point out that the perception of symmetric stimuli is less vulnerable to cerebral insult than the perception of asymmetric stimuli.

The schizophrenic children with positive face-hand test results tended to show low Stanford-Binet IQ's and low mental age. The face-hand test responses, like the intelligence test performance, may be said to reflect the level of general integration. This experiment does not specifically answer the question whether or not diffuse brain disease is the etiological agent in schizophrenia of childhood.

The responses of schizophrenic adults to the face-hand test have been shown to be similar to those of normals and significantly different from adults with severe brain disease. On the other hand, the results for a high proportion of the present group of schizophrenic children differ from those of

normal children of equivalent age and resemble those found in mental defectives and patients with mental changes due to brain dysfunction. What, then, is the relationship between schizophrenic children with impaired perception of double simultaneous stimulation and adult schizophrenics shown generally to be free of this impairment? Is it possible that schizophrenic children with marked integrative defect demonstrated in low intelligence tests and impaired perception of multiple stimuli will ultimately, in adulthood, be differentiated from the adult schizophrenics?

### Summary

In the present study, 16 institutionalized schizophrenic children and 9 institutionalized children with nonschizophrenic behavior disorders, of ages 6 through 9 years, were compared with 94 public school children, ranging in age from 5½ through 8 years, on a test of double simultaneous tactile stimulation, the face-hand test.

The perceptual pattern of both normal and abnormal children is one of face dominance and, where errors are made, hand extinction or displacement. Errors are rarely made on bilateral stimulation of both cheeks or both hands.

By the age of 7 years nearly all normal children are able to perceive both face and hand stimuli within 10 trials. The schizophrenic children, as a group, are significantly different from the normal children and the children with nonschizophrenic behavior disorders in that they failed to identify the hand within 10 trials even when tested with the eyes open. Their pattern of perception is similar to that seen in younger children and patients with mental changes due to severe brain disease. The schizophrenic children with defective perception generally show retarded IQ and mental level as measured by the Stanford-Binet Scale. The relationship of both face-hand and intelligence test results to general integrative level is stressed.

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# Comparative Study of Blood Ceruloplasmin in Schizophrenia and Other Disorders

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Recently a number of reports have appeared pertaining to a disturbance in the metabolism of the aromatic amines in the blood of schizophrenics. With such substrates as *N,N'*-dimethyl-*p*-phenylenediamine (MPD)<sup>1</sup> or adrenaline,<sup>2</sup> it has been possible to demonstrate a greater oxidation of these amines in the serum of schizophrenics. In both instances the oxidation was attributed to a copper-containing protein, ceruloplasmin. At the time the present work was completed we were not aware of the details of Akerfeldt's method except that MPD was a substrate. The present study reports findings on the ceruloplasmin activity of serum from patients with schizophrenia and a variety of other disorders; and the technique used, although similar to Akerfeldt's,<sup>1</sup> appears to be somewhat simpler and subject to fewer errors.

## Methods and Material

Details of our procedure were as follows: To 0.1 ml. of serum was added 1.0 ml. of tris (hydroxymethyl)aminoethane buffer (0.1 M at pH 6.8) and 0.1 ml. of freshly prepared phenylenediamine (PD) (0.1%). After incubation for one hour at 37°C, 2.0 ml. of distilled water was added to the mixture and the optical density measured immediately at 490m $\mu$  on the Beckman spectrophotometer, Model B. Many determinations were made with the dihydrochloride of MPD, in which case the time of incubation was 15 minutes and the wave length was 550m $\mu$ . The blood was used within three hours after being taken, during which time the ceruloplasmin activity did not vary, provided the serum was kept ice-cold. Ceruloplasmin was purified by the method of Holmberg and Laurell.<sup>3</sup> Paper electrophoresis of serum was done

with 0.05 M barbital sodium U.S.P. pH 8.5 at 5°C. The paper was air-dried and then sprayed with a 0.02% solution of MPD in 0.2 M acetate buffer at pH 5.5. A corresponding chromatogram was sprayed with 0.05% bromophenol blue in acetone for comparison of serum proteins. These and other procedures will be published in detail later.

The results on the ceruloplasmin activity of serum were arbitrarily classified into five groups: Group 0, no oxidation of PD; Group I, an optical density of 0.100-0.150 against a water blank; Group II, an optical density of 0.150-0.250; Group III, 0.250-0.350; Group IV, greater than 0.350. Among the diverse number of medical conditions, the greatest number of "positive" reactions (the sum of the last three groups) occurred in pregnancy and schizophrenia (Table I). The incidence of positive reactions was slightly more in pregnancy, but the fraction falling into Group IV was appreciably greater than in schizophrenia. Patients with severe mental retardation and psychomotor epileptics, although considerably fewer than schizophrenics, had a high incidence of "positives," whereas patients with multiple sclerosis fell into Group 0.

TABLE I.—Distribution of Ceruloplasmin in Serum from Schizophrenics and Other Patients\*

Diagnosis	No. of Cases	Group (per Cent of Total)					Sum of II-IV
		0	I	II	III	IV	
Schizophrenia†	252	8	26	34	15	17	66
Pregnancy (7-9 mo.)	18	17	11	22	22	28	72
Neoplasms	39	33	26	17	9	15	41
Mental retardation	175	58	14	16	9	3	28
Psychomotor epilepsy	119	37	40	22	1	0	23
Medical (other)	108	65	17	11	5	2	18
Epilepsy (other)	31	61	32	7	0	0	7
Multiple sclerosis	10	10	100	0	0	0	0
Normals	101	79	18	3	0	0	3

\* Values expressed as per cent of total number.

† The schizophrenics were largely hospitalized patients.

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TABLE 2.—Effect of Various Inhibitors on Ceruloplasmin Activity of Human Serum\*

	Activity γM PD Oxid./Hr.	Per Cent Inhibition
Control	0.40	—
Ascorbate, $10^{-4}$ M	0.10	75
NaCN, $10^{-4}$ M	0.15	65
Hydroxylamine $5 \times 10^{-4}$ M	0.15	65
Semicarbazide $5 \times 10^{-4}$ M	0.10	75
Methyl hydrazine $10^{-4}$ M	0.25	38
Chlorpromazine $10^{-4}$ M	0.20	50
Rescinamine (Rauwolfia derivative) $10^{-4}$ M	0.26	38

\* Reaction consisted of 1.0 ml. tris buffer (pH 6.8), 1.0 μM PD, and 0.1 ml. of schizophrenic serum.

With the exception of patients with neoplasms (carcinoma, but not sarcoma), among whom 41% were "positive," the incidence of positive reactions in a broad spectrum of medical disorders (liver disease, diabetes mellitus, kidney and vascular disease, and severe inflammations) was relatively low. There are a sufficient number of borderline cases (Group I) in all categories studied to alter somewhat the final interpretation of the results; furthermore, the present list of disorders is hardly exhaustive, and further investigation will very likely yield a significant number of "positives" in other categories. The highest ceruloplasmin activity occurred in neoplasms and pregnancy.

A number of various inhibitors of the reaction are presented in Table 2. It is of particular interest that many of the agents are carbonyl-reacting inhibitors of diamine or monoamine oxidase.<sup>4</sup> With the exception of cyanide, which reacts with the copper of ceruloplasmin, most of these agents probably combine with the free radical of PD, which is responsible for the color reaction:



Evidence for the belief that the serum oxidase is ceruloplasmin is presented in Table 3. In general, the pH and temperature dependence of the serum and of the purified ceruloplasmin are nearly identical. Electrophoretic separation indicates that the

TABLE 3.—Evidence for Serum "PD or MPD Oxidase" \* Being Ceruloplasmin

	Comment
Purified ceruloplasmin	Same reaction with PD or MPD; pH and temperature curve identical
Paper electrophoresis	Activity related to α-globulin
Dialysis against NaCN	Activity lost; restored with $\text{Cu}^{++}$ but not with $\text{Fe}^{+++}$
pH	Optimum is 5.5; $\text{Cu}^{++}$ oxidation of PD is not pH-dependent within same range
Relation of $\text{Cu}^{++}$ content to activity	In general, good
Substrates	PD, MPD, epinephrine (adrenaline), serotonin, tyrosine, dopa, naphthol
Oxygen	Proceeds more rapidly in absence

\* PD = phenylenediamine; MPD, N, N'-dimethyl-p-phenylenediamine.

"oxidase" appears in the α-globulin fraction. Both the purified ceruloplasmin and the serum attack a variety of substrates, as reported by Holmberg and Laurell.<sup>5</sup> Inasmuch as the reaction proceeds anaerobically and is not reactivated by  $\text{Fe}^{+++}$  after dialysis against cyanide, it cannot be cytochrome c. There is some suggestion that histamine is attacked by the serum oxidase, but, since this, too, occurs anaerobically, diamine oxidase<sup>4</sup> does not seem to be involved. Although endogenous ascorbate is a potent inhibitor of ceruloplasmin and does interfere in both Akerfeldt's<sup>1</sup> and Leach's<sup>2</sup> procedures, it is apparently destroyed within a few minutes under the conditions of our procedure, as a result of the low serum content and traces of copper in our reagents.

The significance of elevated ceruloplasmin in various neurological disorders,<sup>6</sup> pregnancy,<sup>7</sup> schizophrenia, and neoplasms is entirely unknown. Since a number of neurohumoral amines are attacked by ceruloplasmin, it is conceivable that a disturbance in the metabolism of such substances as adrenaline, serotonin, and histamine may lead to disturbances, including some in schizophrenia. Both the oxidation products of adrenaline<sup>8</sup> and serotonin<sup>9</sup> have been shown to produce toxic reactions. Although it would appear unlikely that an excessive destruction of such amines by serum could be responsible for psychotic disturbances, the metabolic disorder may at least be a reflection of some more significant disturbance within neural tissue itself. In this

connection an elevation in the monoamine oxidase of the globus pallidus of schizophrenics was reported some time ago.<sup>10</sup> Of possible significance is the fact that chlorpromazine and some Rauwolfia alkaloids (rescinnamine) are potent inhibitors of the serum oxidase. Whatever the nature of the oxidative system involved in the present study or the factors responsible for its elevation in schizophrenia and other pathological conditions, the fact that the system may influence the levels of neurohumoral amines within the body warrants further exploration of the problem. Although these studies are only preliminary and only relatively few categories of pathological conditions have been investigated, it is already apparent that the enzymatic measurement in serum has little, if any, value as a "diagnostic test" for any disorder, including schizophrenia.

Dr. R. H. Maschmeyer, of Logansport State Hospital, Logansport, Ind.; Drs. B. S. Osadca and S. Siaroff, of Dixon State School, Dixon, Ill., and Drs. F. Stamps and D. Baldwin, of the University of Illinois College of Medicine, supplied blood samples and diagnoses.

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# Preoperative Emotional States and Adrenal Cortical Activity

*Studies on Cardiac and Pulmonary Surgery Patients*

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Although it is widely accepted that the central nervous system is involved in the regulation of secretion of pituitary adrenocorticotrophic hormone (ACTH), little is known of the relationships between specific emotional responses and the release of ACTH. Since the pituitary-adrenal system is generally stimulated under conditions in which the integrity of the organism is threatened, it might be expected that fear or anxiety most likely would be associated with increased ACTH release and subsequent increased secretion of adrenocortical hormones. Some studies have been made of both psychological and endocrine factors in human subjects during grossly threatening life situations.<sup>1,2,4,6,13</sup>

As in other, previous studies, the initial hypothesis in this study of patients about to undergo cardiac or pulmonary surgery was that there would be a close relationship between the degree to which a patient was anxious and the plasma levels of his adrenocortical hormone. Attempts were made to predict this hormone level on the basis of the extent to which a patient, awaiting major surgery, was anxious. However, exploratory experience indicated that, although energy and affect are mobilized in a person to meet such stressful situations, the observable af-

fect which correlated with adrenal hormone levels was not always anxiety. It was found that a number of emotional states in a heightened form were associated with elevated adrenal steroid hormone levels. This included such states as hostility, agitated depression, apprehension, etc., with the exception of withdrawn depression.\*

From the data obtained, it appeared that what was crucial in studies of this kind was the evaluation of the amount of general emotional involvement† that a person had in a given situation, and not merely the degree to which he demonstrated "anxiety." Emotional involvement was considered the investment of active feeling by the subject at the time in a direct interaction with a person or persons.

It is suggested that the pituitary-adrenocortical system may be associated with a number of emotional states, which seem to have a common component of emotional involvement. This component may be a relatively broad, undifferentiated state un-

\*The depression to which we refer is the flat, resigned, apathetic type, and not one of agitation or intense grief. Both the latter forms of depression have highly active emotional involvement components.

†It is hoped that the term "emotional involvement" will be descriptively self-explanatory. What we have in mind are things such as the impression of the observer that the interaction pattern which the subject tries to engage in or set up with other persons is characterized by directness, intensity, all-or-none qualities, and immediacy. These may be demonstrated through any modes of communication, i. e., verbal, gestural, or autonomic manifestations, with emphasis on the immediacy and directness of the emotional involvement.

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Major Paul Schafer (MC), U. S. Army, Chief of the Thoracic Surgery Section, Walter Reed Army Hospital, and his staff, cooperated in this study. Dr. David Rioch, Walter Reed Army Institute of Research, made suggestions and contributions to this project.

TABLE 1.—Final Diagnoses of Twenty-Four Thoracic Surgery Patients Studied

Rheumatic valvular heart disease.....	5
Interatrial septal defect.....	1
Coarctation of aorta.....	2
Patent ductus arteriosus.....	1
Fibrous pericarditis.....	1
Bronchiectasis.....	5
Spontaneous pneumothorax.....	1
Pulmonary cyst, granuloma, and tuberculoma.....	6
Mediastinal sarcoidosis.....	1
Benign rib osteoma.....	1

derlying or accompanying a number of emotions.

The present report was based upon concurrent observations of emotional status and adrenocortical hormone levels as measured by the relatively specific index of plasma 17-hydroxycorticosteroid concentration. Emphasis was placed on obtaining the psychiatric and psychological observations and the samples for hormone analysis as close together as possible, usually within a period of a few hours on the morning of the day before surgery.

### Subjects

Patients were randomly selected from the thoracic surgery wards of Walter Reed Army Hospital. However, only those who met certain physiological requirements were included in the correlative aspects of this study. Patients who had any of the following conditions were excluded: (1) active, severe infection, (2) malignancy, (3) endocrine disorder, (4) menstruation, and (5) central nervous system drug intake.

Table 1 presents the final diagnoses of the 24 patients who met the physiological criteria,† with the number of patients in each category.

With the exception of the patient with the rib osteoma, all had operations on the heart, lungs, or aorta.

The mean age of the men in the group studied was 23 years (range 19-47 years). For the 6 women, the mean age was 28 years (range 20-38 years).

Three sets of data were obtained from these patients: (1) psychiatric interviews, (2) psycho-

† Adrenal hormone levels were obtained on a total of 80 patients over a two-year period. Of these, 63 met the physiological criteria listed above. The psychiatrist studied 62 patients, and the psychologist tested 33. The 24 patients reported here are those subjects who met the criteria and who were evaluated by all three members of the research group.

logical test responses, and (3) adrenocortical hormone levels.

### Method

Diurnal blood samples were obtained over a period ranging from 21 days before surgery to the morning of surgery. All subjects reported here had blood samples drawn on the day prior to surgery. The heparinized plasma was analyzed for free 17-hydroxycorticosteroid concentration by the method of Nelson and Samuels.<sup>7,8</sup> Eosinophils were counted by the wet chamber method of Randolph,<sup>11</sup> and the total white cell count, hematocrit, and sedimentation rate were also determined on each sample. Blood samples were routinely obtained between 8 and 9 a.m. and between 3 and 4 p.m. Twenty-four-hour urine samples were collected in two twelve-hour aliquots, beginning at 8 a.m. The total urinary 17-hydroxycorticosteroid excretion was determined by the Glenn-Nelson method.<sup>6</sup>

Also, the day prior to surgery, the patients were interviewed by the psychiatrist and tested by the psychologist, usually in the morning. The interview, of a fairly standard nature, was tape-recorded. The interview was directed toward securing an impression of what the patient was experiencing regarding the forthcoming surgery. Seldom was a detailed psychiatric history sought, and the interview was not designed to be psychotherapeutic or informative medically to the patient. No attempt was made to disturb or question the defensive adaptations of the patient, nor were interpretations frequently made. Immediately after the interview, a notation was made describing the patient's behavior and demeanor during the interview, and a rating was made of the extent of discomfort or emotional involvement§ which the patient appeared to be experiencing. An eight-point rating scale was used. A rating of 1 indicated little or no detectable discomfort-involvement and a low level of immediate affective involvement, whereas a rating of 8 indicated marked discomfort or high emotional involvement. Both psy-

§ In the initial phases of this study "anxiety" was rated. For reasons already alluded to, and to be explained more fully in the body of the paper, this rating was changed to a "discomfort-involvement rating," since this was a truer reflection of what was being measured. In personal communication with Dr. David Hamburg, Michael Reese Institute for Psychiatric Research, this group has adopted the term "distress" for use in similar psychophysiological studies. This group has considered adrenocortical functioning to be related more closely to a broader range of conditions, designated by the term distress, than to the narrower range, designated by the term anxiety.

chiatrist and psychologist used this scale to rate the total behavior noted in the specific, limited observation periods. Because the correlation of the psychiatrist and the psychologist was highly significant, it can be assumed that they were rating the same phenomenon.

The psychologist administered the Rorschach Test, four Thematic Apperception Test cards, and the Emotional Projection Test<sup>16</sup> and used a series of projective stories in which common doctor-patient interactions were depicted in order to explore the extent of emotional involvement the person had in the current interactions between himself and the physicians caring for him.<sup>16</sup> Attention spans were measured by auditory and visual retention tests.

The three investigators kept their data and impressions separate from one another until each had made his final evaluation. The psychiatric and psychological test ratings were then correlated with the hormone findings.

## Results

**Biochemical Findings.**—Although the detailed biochemical data appear elsewhere,<sup>7</sup> some of the principal findings are summarized here.

The mean plasma 17-hydroxycorticosteroid value determined for the 63 patients at 8 a.m. on the day before surgery was 17.7 $\gamma$  per 100 ml. of plasma (range 8 $\gamma$ –27 $\gamma$  per 100 ml.). This was significantly higher than the mean value of 12.0 $\gamma$  per 100 ml. obtained on normal subjects in our laboratory. In 14 of the surgical patients from the above group on whom several measurements could be made during the week prior to surgery, there was a trend toward higher

plasma and urinary hydroxycorticosteroid values as surgery approached.

Table 2 summarizes the 8 a.m. plasma 17-hydroxycorticosteroid values obtained on normal subjects and on subgroups of patients in the present study. It was of particular interest that patients rated 6-8 on the rating scale of discomfort-involvement by the psychiatrist and psychologist showed mean plasma levels of 21 $\gamma$  and 23 $\gamma$  per 100 ml., respectively, as compared with a mean of about 18 $\gamma$  per 100 ml. for the group as a whole. In the two subgroups in which physiological damage was present, i. e., patients with chronic disease (principally malignant neoplasms) and the patients with repairing thoracic wounds in the third- to the seventh-day postoperative period, it was apparent that levels were maintained no higher than those observed in patients with high discomfort-involvement ratings. From these findings, as well as those in current related studies, it began to appear that, although peak plasma 17-hydroxycorticosteroid values, ranging up to 70 $\gamma$  per 100 ml. or above, may be reached in certain acute stress situations, such as during major surgery, levels in the range of 20 $\gamma$ –30 $\gamma$  per 100 ml. may represent significant increases in adrenocortical activity in situations where the stressful circumstances continue over a period of days or weeks or longer.

The diurnal variation in 17-hydroxycorticosteroid levels showed remarkably constancy of direction, with afternoon levels

TABLE 2.—Plasma 17-Hydroxycorticosteroid Levels in Normal Subjects and Certain Subgroups of Surgical Patients \*

Normal	Preop. 3-7 Days	Preop. 1 Day	Admission to Hospital	Anxiety 6-8† (Psychiat.)	Anxiety 6-8† (Psychol.)	Chronic Organic Disease	Postop. 3-7 Days
10	22	22	27	27	26	20	27
13	18	14	24	26	24	19	25
9	11	9	20	25	23	24	23
14	13	14	21	23	22	18	20
12	16	14	20	22	21	24	22
13	10	13	15	22	20	12	23
11	21	21		21			23
15	23	23		20			13
4	10	19		18			
10	10	18		17			
20	14	22		15			
14	15	18		10			
14	15	26					
		13					
Mean values 12	15	18	21	21	23	20	22

\* All samples were drawn at 8 a.m. Values are expressed in micrograms per 100 ml.



TABLE 3.—Correlations Between Psychiatrist's and Psychologist's Discomfort-Involvement Ratings and the 17-Hydroxycorticosteroid Levels

Raters	Correlation Coefficient
Psychiatrist's rating	0.462*
Psychologist's rating	0.590*

\* Significant at the 5% level of confidence or better. The correlation of the psychiatrist's and the psychologist's ratings was significant ( $r=0.65$ ;  $P<0.05$  or better).

averaging about 40% lower than morning levels, even on the day before surgery. In several cases the diurnal drop appeared to be exaggerated, with afternoon levels as much as 90% lower than morning levels. In the group of 15 patients on whom concurrent blood and urine 17-hydroxycorticosteroid measurements were made, a mean urine excretion value of 5.65 mg. per 24 hours was obtained, with individual values ranging from 2.90 to 11.30 mg. per 24 hours. Levels in any given patient were within a relatively narrow range from day to day, but values became sharply elevated in several patients the day before surgery.

**Psychiatric-Psychological.**—The correlations of the ratings and the 8 a.m. steroid value of the day before surgery were significant and are summarized in Table 3. Correlations were also made between the ratings and two other steroid values; the mean of all diurnal measurements from admission to the hospital to the time of surgery, and the mean of all 8 a.m. levels throughout hospitalization. These correlations were not as high as those between the rating and the single 8 a.m. value of the day before surgery. From this, it would appear that the obtaining of all data at approximately the same

time is important, corroborating our impression that one significant aspect of a collaborative study of this type is the temporal factor.

Of the eight patients whose steroid values were 20 $\gamma$  per 100 ml. or higher the day prior to surgery, the psychologist gave six patients a discomfort-involvement rating of 6 or more; the psychiatrist rated five patients in Category 6 or higher. Both investigators classified the same two subjects lower than the steroid level would have indicated, and the psychiatrist, one other person in addition. Thus, it appeared that most of the patients with high steroid levels (20 $\gamma$ -27 $\gamma$  per 100 ml.) tended to display behavior and have associations suggestive of marked states of discomfort and emotional involvement.

Table 4 shows that the anxious content alone on the Rorschach test did not reflect the adrenal hormone levels. The four scorings which correlated significantly with the steroid values were (1) unpleasant content, (2) affect-tinged associations (non-neutral content), (3) introversive tendencies, and (4) associations not purely logically directed ( $F+%$ ). Specifically, persons with high steroid levels tended to give high amounts of unpleasant content, which was the total per cent of hostile, anxious, and bodily preoccupation associations.<sup>3</sup> Those with high steroid levels also tended to give few neutral associations, have lower amounts of clearly seen responses ( $F+$  lower), and the occurrence of more human-movement than color responses in the Rorschach "experience balance." These findings suggest that in this group there were relationships between steroid levels and those features of the Rorschach responses which revealed the over-all amount of associations tinged by various emotional components. As shown in Table 4, anxious content did not correlate with the steroid levels. In summary, the greater the emotionality and the involvement with the environment, the higher were the steroid levels.

TABLE 4.—Correlations of Psychological Test Scores and Steroid Levels

	r
Rorschach affective symbolism	
Hostile content	0.148
Anxious content	0.222
Body content	0.253
Unpleasant content	0.464*
Dependency content	-0.215
Positive content	0.329
Neutral content	-0.602*
Form per cent on Rorschach	0.014
Extended $F+%$	-0.526*
Introversive tendencies	0.622*
Auditory digit span	0.012
Visual attention span	0.320

\* Significant at the  $P<0.05$  level or better.

It was evident also from the psychiatric interviews that there was no characteristic manner of psychological adaptation to the forthcoming surgery. The emotional responses were diverse. Some persons viewed the surgery as a step, though a dangerous and unpleasant one, toward a "new lease on life," in which activities denied them for some time would be possible. This was especially true for some of the rheumatic heart disease patients. Other patients were particularly concerned about the surgical risk and about dying, to the exclusion of any other possible factors. Some were embroiled in angry, resentful states in their personal lives which seemed to be carried into the hospital situation. These persons had high states of emotionality, but not always anxious ones.

As the study progressed, we found ourselves using the term "discomfort" rather than anxiety in assigning ratings to the patients; this, we believe, reflected an impression that anxiety as a clinical entity was not the sole axis in the psychophysiological system of hormone regulation. In scrutinizing the data of those subjects for whom there was a great discrepancy between the rating and the hormone level, we realized that some of these persons were not anxious in a clinical sense but were, for example, actively hostile, either covertly or overtly, and low anxiety ratings had been given them, whereas the hostility itself was an active, alerted state experienced by the patient as uncomfortable.

Thus, it appeared that the 17-hydroxycorticosteroid concentrations were associated with a variety of emotional states and were thought to be a reflection of the degree to which a person was interacting with his immediate environment, no matter what his affective state was.

While the emotional responses to the current hospital situation were extremely individual and varied, some general observations may be made. Three types of behavior frequently emerged as adaptive patterns. These were (1) to assure oneself

that the surgeon had the greatest capabilities, (2) to avoid communicating the seriousness of the surgery to parents, and (3) to project fears and doubts and to discuss them as if they belonged to someone else.

Fifty-two per cent of all the patients expressed strong feelings about the superlative capabilities of the surgeons, referring to them as the "best surgeons in the world," at the same time not knowing specifically who was going to do the surgery and at times naming the cardiologist as the chief surgeon. Many of these same patients had specific complaints about not seeing the doctor, learning the date of the surgery from the ward secretary, and so forth; yet they seemed to maintain tenaciously what we have termed a magical reassurance about "the surgeon."

Of the 17 single men in the group seen by the psychiatrist, 9 had not informed their parents of the forthcoming surgery. Six others had grossly understated the seriousness of the operations or were misleading in the information they gave their parents. Only two gave unqualified information about the surgery. Thus we saw an almost consistent trend among the single men to face this current situation alone, without their parents' knowledge, presence, or support. The stated reason was a desire not to worry their parents, but the content of associations indicated a desire to avoid complicating emotional involvement with parents at this crucial time. It was as if the situation was stressful enough without having concerns about how the family would react and having this further load of affect to handle.

Another observation was that the spouse or some member of the family was described as more anxious than the patient and as having expressed thoughts which the patient felt alien to himself, such as "I have complete faith in the surgeons, but my husband says they're only human beings and they can make a mistake." Indeed, the anxiety of the spouse was often confirmed by ward personnel, and even more strikingly by recovery

room nurses, who remarked about the intensity of the spouses' concerns. However, it appeared that many patients projected their preoperative concerns onto their spouses or other relatives.

It was noteworthy that 60% of the subjects with steroid levels above 20 $\gamma$  per 100 ml. stated that some member of the family was worried about the surgery, whereas only 48% of the patients with steroid levels below 20 $\gamma$  per 100 ml. stated this.<sup>||</sup>

The Doctor-Patient Stories were helpful in assessing the total emotional state of the person and for direct comparison with attitudes expressed in the psychiatric interview. The most significant aspect of these stories was that the majority (all but two) of the patients handled them in a personal rather than in an abstract manner. It was thought this indicated greater interaction with persons in the immediate situation than was found in groups of medical patients hospitalized for cardiovascular and gastrointestinal diseases, who treated the stories in an

impersonal style and rarely made direct references to their own current situations.<sup>14</sup> (The two surgical patients who did not treat the stories in a personal way were depressed.)

### Clinical Diagnosis and Case Summaries

Diagnostic clinical impressions fell into five major groups:

Normal	10
High-discomfort states	6
Depression	3
Schizophrenia	3
Character disorders	2

For the sake of brevity, we have grouped together patients with such diverse diagnoses as anxiety reaction, passive-aggressive reaction, phobic reaction, etc., into the category of "high-discomfort states." The six persons in this category were among those with the highest steroid values, although, as indicated previously, several people diagnosed as normal had elevated steroid values also. By the term "high-discomfort states" we wish to convey the impression that the clinical diagnosis was of relatively little importance when contrasted with the amount of feeling evidenced in the current situation. Also, it was our impression that the affect which was clearly associated with interaction in the current situation outweighed the presence of such classical anxiety signs or symptoms as perspiration, tremor, palpitation, sighing, etc.

It was of note that the adrenal cortical activity of the three people with a diagnosis of schizophrenia was within normal range as measured by the plasma 17-hydroxycorticosteroid concentration. While the number of subjects was small, the adrenal-output findings suggested that schizophrenia and

<sup>||</sup> Another significant correlation was found, but, because its meaning has remained unclear to us, it is reported in abbreviated form. The recorded interviews were analyzed for the occurrence of negative words, spoken by the patient and the doctor. The difference between patient's and doctor's negative word percentages correlated  $-0.501$  with the steroid level, a result which is significant at the 0.05 level of confidence or better. Thus, the smaller the difference between negative word percentages of the patient and the doctor, the higher the steroid value tended to be. The frequent use of negative words by some patients did not seem to be a reflection of the denial mechanism. One hypothesis was that the psychiatrist assumed a more cautious approach to those patients who appeared more emotionally upset and tended to do more mirroring of these patients' remarks than he might have otherwise.

TABLE 5.—Correlations of the Biochemical and Psychiatric-Psychological Findings in Preoperative Patients

	Plasma 17-Hydroxy- corticosterone	Psychiatrist's Anxiety Rating	Psychologist's Anxiety Rating	% Neutral Responses Rorschach	% Difference Negative Words
Plasma 17-hydroxycorticosteroid	..	0.46*	0.57*	-0.60*	-0.50*
Psychiatrist's anxiety rating	..	..	0.65*	-0.36*	0.05
Psychologist's anxiety rating			..	-0.76*	-0.25
% neutral responses Rorschach				..	0.41
% Difference negative words					..

\* Significant at 0.05 level.

low adrenal functioning were not always associated.<sup>10</sup> Recent studies by Bliss et al. have demonstrated this also.<sup>1</sup> Our observations would lead us to correlate the extent of a schizophrenic patient's emotional interaction with others and his steroid level. The hypothesis would be that those who are flat and apathetic and have very little emotional investment in those around them would have lower steroid levels than those who make more active emotional participation with their environment.

It was particularly noteworthy, in view of recent work with cardiac surgery patients,<sup>5,15</sup> that in this series of 24 patients (and in the larger group evaluated by the psychiatrist) amnesic reactions were not found, nor were conversion reactions or dissociated or euphoric states. This finding was applicable to both the preoperative studies and the short postoperative contacts made by the psychiatrist.

The following summaries illustrate the case material.

*Normal*—A married woman in her mid-20's had had rheumatic heart disease from the age of 9 years. She talked freely and showed little overt anxiety, although she referred to times when she had felt anxious. She saw surgery as a step toward "becoming normal and all right," and was eager to get it over because she "knew she'd feel better afterwards." She had a clear picture of the surgery, even calling the commissurotomy procedure by the surgeon's term of "fracture."

She tended to minimize her physical condition, for example, by saying she had a "fairly normal childhood," in the face of frequent bouts of fever, prolonged absences from school, severe exertional dyspnea, and so forth. She forgot to take digitalis and to renew her supplies of the drug, and casually went about her business. However, she was able to permit others to help her. At school, when short of breath, she had friends carry her books. On a job, she let her supervisor do a little extra work when she was "weak." Both the interview and the projective tests indicated that being dependent was not a problem to her and that she could use others' help without conflict. She seemed aware of this, and further stated she felt God "would see that things worked out" on the surgery, even though it was a serious operation. She was rated in the low-discomfort group (2 by one observer; 1 by the other), and in her adrenal steroid level she was among the lowest in the group, 12γ per 100 ml.)

*Normal with Compulsive Trends*—A 21-year-old single man was admitted to the hospital on two occasions eight months apart for lobectomies in treatment of bronchiectasis. He was seen both times by the psychiatrist and on the last admission was tested by the psychologist.

In both interviews he repeatedly stressed his difficulty in initially convincing a doctor he needed treatment for his cough and his feeling that others thought he was trying to get out of work. He expressed resentment and bitterness toward a doctor at another hospital who he felt had caused his lung trouble. This same theme was an outstanding feature of his Doctor-Patient Stories.

During the second hospitalization he was obsessively concerned about a patient who had a thoracotomy drainage tube in place for five weeks (in contrast to the usual two or three days). In association with this, he recalled a dream in which a corpsman had awakened him at night in the recovery room and had wrapped a towel around him, trying to make him cough. He said this dream made "every little bit about the first operation come back."

His ambivalence toward his first surgeon was expressed by his saying that someone had called the doctor a butcher, but he personally liked the surgeon. He went on to say that his scar was wider than other patients', that he felt freakish in swimming trunks because the one time he had gone swimming people stared. He thought the second scar, on the other side, would "even things up."

For his first surgery, he had said that he was not going to inform his mother of the operation and had made detailed plans to have another patient telephone her the evening of the surgery. However, the night before the surgery he called her but forbade her to come to the hospital because she would just get upset. She told him then that he didn't need the operation. Again, at the second operation, he would not permit her to visit him.

On testing, his associations suggested that few thoughts emerged affect-free. He appeared to have compulsive defenses, indulging in constant activity or obsessive planning, and he was a chronic worrier.

His steroid level placed him at the low end for the group (13γ per 100 ml.). He was rated by the psychologist as more discomforted (5) than his steroid concentration would indicate. The psychiatrist rated him 3. It would seem that the compulsive thinking and activity worked rather efficiently as a tension reducer and that this was not evident on psychological testing.

*High-Discomfort State*—A 38-year-old married woman with a congenital interatrial septal defect had an extremely apprehensive facial expression. Her manner of speaking was a peculiar mixture of incomplete sentences and thoughts, syntactical

and grammatical errors, and nonverbal sounds, punctuated by frequent laughter. Her discomfort seemed to find its most flagrant display in her mode of verbal communication, with little evidence of other clinical signs of anxiety, except her facial expression. Her husband had brought to her attention her peculiar way of talking since coming into the hospital, mainly by enjoining her to finish stories she had started.

Denial mechanisms were prominent, especially in reference to the heart defect. She stated that after marriage, prior to which she had maintained restricted activities, she "just started doing a lot of things. I wanted to ignore the heart condition, but the doctor said that I couldn't."

She felt her husband was covering up his concern over the surgery. He had been interested in learning what the surgical mortality rate was; when he was told by the surgeon that if his wife died the rate would be 100%, she remarked she thought these words were "wonderful," and that they had a reassuring effect on her husband.

On testing, she was preoccupied with what the surgeons were going to do to her body and with concerns that she might die. Her anxiety was so severe that she was unable to keep her attention focused.

She was rated among the highest (7) by both observers on the discomfort scale, and, likewise, her steroid level was among the highest (26 $\gamma$  per 100 ml.).

*High-Discomfort State with Compulsive Trends.* A 37-year-old married sergeant with bronchiectasis was superficially pleasant; there was a great amount of excessive body movements, and he appeared quite tense. He repeatedly expressed the concern that if he was not fully unconscious in the operating room he "was going to fight that knife." He associated with this a long history of fear of knives and of being knifed, and secondarily of hypodermic needles and dental work.

He attempted to give the impression that his surgery was nothing to be concerned about: "My folks worry about me, but I've assured them I wasn't worried. My wife is worried about me; but there is nothing to fear, I told her." He suppressed his concern of being physically handicapped the rest of his life from the removal of lung tissue. On psychological testing he was found to be overly independent, cynical, and hard-working. Forty-three per cent of his Rorschach content was scored as anxious, with only 13% neutral responses. The Doctor-Patient Stories demonstrated his concern over fighting the doctors in their evaluation and treatment of him. He was told this story: "A man was going to have an operation. He became upset one day. Why? How did he feel about it, and what did the doctor do and why?" He responded: "When they did the bronchoscopy, I was scared to death. I cried like

a baby because they made me so mad. Not knowing what it was about made me scared. I spit it up four times. The doctor got very angry. I was as angry myself. If he had just sat down and spent five minutes telling me what it was for, it wouldn't have been so hard." However, by contrast, when talking to the psychiatrist, he said he was not going to talk to the surgeons, that he didn't have any questions he wanted to ask them. "I don't know what they're going to do, or how, and I don't want to know. Just get it over with."

This man was given a discomfort-involvement rating of 6 by both observers, and his steroid level was likewise elevated (22 $\gamma$  per 100 ml.).

*Depression.*—An enlisted man, in his late 40's, had been admitted to the hospital for persistent complaints of pain related to minimal osteoarthritis of the spine. Upon discovery of a coin lesion on routine chest x-ray, he was transferred to the thoracic surgical service. His surgery was postponed two weeks because of his having contracted an upper respiratory infection.

He was a compliant person, who seemed eager to please, and he seemed to relate to the examiners warmly but subserviently. He was depressed clinically and by psychological criteria. Prominent on the tests were a pervasive feeling of sadness, worthlessness, bewilderment, and solitude, with a narrowing of attention to only the blatant and mundane events about him. The Doctor-Patient Stories suggested that much of his depression had grown out of feelings that the doctors had not expressed their expectations of him or informed him of the details of his condition. However, in psychiatric interview it appeared that the depression was not a reactive type due to his forthcoming surgery. He said that he had noticed increasing irritability, with concerns about losing his temper, over the past three or four years. During this period he had also experienced heightening of sexual desires, but with decreased powers. An impression of early climacteric depression was made.

He said concerning the surgery: "I just seem to be shaky about it. And the closer it gets, the shakier and more nervous I get. I don't seem to have any fear of anything happening because I think we've got the best doctors here. I have a lot of confidence in them. I wish I could explain to you exactly how I feel. I believe if I knew more about what they were going to do in there, that it may help me a lot. But I don't know whether they're going in there to take the lung out or what. All I know is that I am going to get surgery on a lung." He said he had been waiting around every day for the doctors to call him in, but no one had done so. However, he had not asked to see the surgeons because he felt this might be interpreted as an expression of anger toward them which would gravely jeopardize his

care. He expressed great bitterness that his arthritis, for which he had entered the hospital, had not been treated and repeated the same complaint that no one had told him anything, nor had he asked. He seemed to handle irritation and anger by avoidance and suppression techniques.

He was rated mid-low (3 by one observer and 2 by the other) on the discomfort-involvement scale, and low steroid values were found (12 $\gamma$  per 100 ml.).

*Schizophrenia*.—A 28-year-old single man with a bronchogenic cyst was diagnosed as a paranoid schizophrenic by the two observers. Although understandable, most of his remarks were extremely cryptic. At times he became confused about dates. He demonstrated a well-organized delusional system which centered about a camera-gun he said he had invented.

Although during the psychiatric interview there were only two references to his doctors (they were the best surgeons in the world, and the doctors seemed a little bit on edge when he told them he had no relatives he wished informed of the forthcoming surgery, not even his father), on testing he revealed many intense feelings about the doctors, whom he felt had lied to him in under-emphasizing the seriousness of the surgery and who, if he established a friendly, confiding relationship with them, would eventually leave him. These active concerns about the trustworthiness of his physicians seemed to be a focusing of his rather basic distrust of people and his fears of being deserted. He indicated he was frankly frightened of the surgery, especially because his mother had had removal of a breast tumor, first thought to be benign but finally diagnosed as carcinoma, and of which she died several years later. He said his fear of the surgery was a "throw-back" to his feelings about his mother, and he was afraid the same course might happen to him.

He was placed in the mid-low group of discomfort-involvement rating (3 by one observer and 4 by the other), and his steroid level was at the mean for the group (17 $\gamma$  per 100 ml.).

*Character Disorder*.—A young single man was admitted to the hospital for surgical repair of an asymptomatic coarctation of the aorta, discovered on a routine physical examination. He gave a long history of acting-out and antisocial behavior; he had a police record as a juvenile and had had several courts-martial.

He was concerned about the size of the incision, and only secondarily with the operative risk. However, the strongest theme, demonstrated both in interview and in testing was his concern over being immobilized after surgery. (This immobilization is in reality rather striking: For several days postoperatively the patient is not allowed any movements of his own; he is fed and bathed

and his teeth brushed, etc., by the nursing staff. Activity is then only gradually resumed.) "I don't like it—the idea of just laying there—you're more or less helpless; they got to feed you the first two or three days; they got to bathe you and shave you—that bothers me. I hate to stay in one spot. I like to move around." Projective tests indicated this man had pervasive sadistic fantasies of a violently destructive nature. Prominent in the interviews was his bitterness at the retaliation of authorities for the "small things" he had done that had provoked disciplinary action.

Like most of the single men in this group, he did not inform his mother of the surgery. "What she don't know, well, she won't worry. My mother worries too easy. Guess this surgery would worry the hell out of her."

He was rated in the low-mid group of discomfort-involvement (4 by one observer and 2 by the other); his steroid level was 14 $\gamma$  per 100 ml.

### Comment

Although patients were initially rated on an "anxiety" scale, it was not possible to demonstrate clinical anxiety in some persons who were given a high rating. The one person classified as having an anxiety neurosis did have the highest steroid value of the entire group seen by the psychiatrist. However, those persons who were considered to be in high-discomfort states on the whole could not be classified as having anxiety neuroses or states. In addition, their projective test responses were not in the main anxious ones; their associations covered a wide range of emotions, such as resentment, pleasure, anger, and dependency wishes, with extremely low amounts of neutral responses. As previously mentioned, those few patients rated lower than 6 on the scale who did have high steroid values were seen to have states of high emotionality, but the affect was not anxiety. In other words, anxiety was not always the predominant affect most clearly and strongly associated with the current situation. Thus, a rating scale based on "anxiety" was misleading, both in name and in purpose.

For these reasons, we moved from measuring anxiety to the more general rating we have termed discomfort-involvement. Discomfort-involvement ratings were based



on (1) the appearance of observable or heightened states of emotionality; (2) the strength of the emotional investment in the current situation, and (3) the degree of distress engendered by the emotional state in the subject.<sup>¶</sup> It can be seen that these features have elements of both discomfort and involvement, either implicit or explicit.

The reactions of these patients awaiting major thoracic surgery were extremely diverse. Few, if any, consistent or typical emotional, character, or defense patterns emerged. What did differentiate the high-steroid group from the low- and middle-steroid group was the appearance of strong, heightened emotional states in the psychiatric interviews and psychological test responses of the subjects in the high-steroid-level group.

It is possible that discomfort with certain feeling states was the "anxiety" that was looked for initially and was the phenomenon that most investigators have used in correlating psychological behavior and physiological measurements. However, attempts at quantification of this particular facet of interaction fell short in predicting steroid levels.

It is probable that both the emotional involvement and the discomfort experienced by the subject in the current situation joined forces and were reflected in the adrenocortical hormone levels. The ratings were an attempt to combine these elements in an over-all measure.

Thus it appeared that the extent to which a patient was experiencing any kind of feeling or affect state was what was crucial in the psychophysiological axis involving the adrenal cortex. The extent of involvement

or active emotional interchanges with others in the current situation was a valuable operational concept.<sup>#</sup> Mild to moderate depression acted as a damper upon this interaction. Any other affective states tended to promote or be associated with varying capacities for involvement with others.

### Summary and Conclusions

A group of patients were interviewed and given psychological tests one day prior to thoracic or cardiac surgery. Diurnal blood samples were obtained over a period varying from 21 days before surgery to the morning of surgery. All subjects had measurements of plasma 17-hydroxycorticosteroid concentrations the day before surgery. A mean of 17.7 $\gamma$  per 100 ml. was found, which was significantly elevated from the normal for our laboratory. Significant correlations were found between discomfort-involvement ratings independently given the patients by the psychiatrist and by the psychologist prior to knowledge of the hormone values. Mean plasma 17-hydroxycorticosteroid levels on patients given discomfort-involvement ratings of 6 to 8 by the psychiatrist and the psychologist were 21 $\gamma$  and 23 $\gamma$  per 100 ml., respectively. Ratings of discomfort-involvement were based upon the over-all impression of the subject's display of feelings and the amount of emotional investment in the current situation.

Significant correlations were found between high steroid values and four Rorschach ratings: low percentage of neutral associations, high percentage of unpleasant content, low form accuracy, and introversion tendencies.

Three frequent adaptive behavior patterns were noted: assuring oneself that the surgeon was ultracapable; single young men evading telling their parents of the approaching surgery, and married subjects re-

<sup>¶</sup>A concept suggested by Dr. David Riech which can be investigated in both human and animal studies is that of evaluating the extent to which the organism is anticipating activity. The various emotional states observed in this study which correlated positively with heightened hormone levels were ones in which the subject was active or anticipating activity, but in withdrawn, passively depressed states, characterized by withdrawal and lacking anticipation of possible action, the hormone levels were low.

<sup>#</sup>This concept of involvement has been used previously to predict successfully the magnitude and type of cardiovascular responses made by subjects during structured, projective interview situations.<sup>19</sup>

porting that family members were more anxious than they and seemingly using this as a device to suppress fear.

Mild to moderate depression was associated with lower steroid values. Two groups of compulsive personalities were noted. If the defenses were working, the steroid levels were not extremely high. However, where the observers noted that the defenses were not effective and heightened but disorganized activity states were noted, high steroid levels were found. A small number of schizophrenic patients had normal steroid values.

It was found that a concept of how anxious a patient appeared to the observers did not prove as useful as the extent to which a patient made active emotional participation with his environment; i. e., his degree of emotional involvement appeared to be a more valuable operational concept in predicting the steroid values than anxiety alone.

The major conclusion suggested by our findings is that the response of the pituitary-adrenocortical system is related to emotional processes, and, further, that it is probably not associated with a single specific emotional state, such as anxiety or fear, but, rather, is associated with a number of emotional states that have the relatively undifferentiated component of distress-involvement.

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# Relation of Physiological and Psychological Effects of Lysergic Acid Diethylamide

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The purpose of this report is to show the relationship that exists between a number of physiological measures and concomitant psychological effects of lysergic acid diethylamide (LSD).

LSD and other centrally acting drugs will produce a variety of physiological and psychological changes in man; however, there has been no attempt to determine whether the persons who show the greater physiological changes also show the greater psychological changes. It is usually assumed that when two subjects receive a drug the subject who shows the greater physiological change will also report that he is more affected by the drug, and that if his behavior were measured he would also show the greater impairment in this behavior. In the present study data will be presented to show that this is only partially true.

## Methods

Ten normal volunteers between the ages of 18 and 23, six male and four female, served as subjects. All the subjects had little or no previous experience with centrally acting drugs. Each subject received 100 $\gamma$  of LSD and, on separate days, two placebos. Both LSD and the placebos were administered orally in identical capsules; the "double-blind" technique was employed throughout. Seventy-five minutes after ingesting the drug each subject received the following psychological tests: addition, both three and nine digits, pursuit rotor, digit symbol test, speed of copying numbers, tachistoscopic discrimination, and tactual perception.

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Scores were expressed as a per cent of the mean of two control scores, and then an overall mean per cent score for all tests was obtained. This score will be referred to as the objective psychological score. The detailed description and results of the effect of LSD on these tests have been previously reported.<sup>1</sup>

In addition, a 47-item symptom questionnaire was given at 30, 90, 150, and 210 minutes after the ingestion of the drug. This questionnaire was specifically designed<sup>2</sup> to elicit the subjective effects of LSD. The score on this questionnaire was the total number of symptoms checked for the four periods. This score will be referred to as the subjective psychological score.

The following physiological measures were recorded at approximately 140 minutes after the ingestion of the drug: pulse, respiration, oral temperature, and blood pressure. These were recorded after the subject had remained supine for five minutes.

Correlations between the extent of each of these physiological measures and the extent of objective and subjective effects of LSD were computed by means of the product-moment method.<sup>3</sup> To test the significance of the difference between the effects of LSD and a placebo, the Dunnett *t*-test was employed.<sup>4</sup>

## Results

Table 1 shows the psychological and physiological effects of LSD and a placebo. All of these LSD scores were significantly different from the placebo scores ( $P < 0.05$ ).

Table 2 shows the correlations between the two types of psychological effects and each of the physiological measures. The subjective effects fail to correlate significantly with any of the physiological measurements, while the objective psychological effects correlate significantly with all the measures with the exception of respiratory rate.

TABLE 1.—Mean Psychological and Physiological Effects of LSD and a Placebo

	Physiological				Psychological	
	Blood Pressure, Systolic	Pulse, per Min.	Respiration, per Min.	Temperature, Degrees (C)	Objective*	Subjective†
LSD	123.4‡	87.6‡	21.4‡	37.9‡	74.0‡	31.5‡
Placebo	110.1	68.7	17.8	36.7	101.9	3.4

\* Per cent of the mean of two control days (the smaller the number, the greater the deficit).

† Mean number of plus responses on the symptom questionnaire.

‡  $P < 0.05$  between placebo and LSD.

### Comment

The results indicate that there is a significant relationship between some physiological effects of LSD and its objective psychological effects. However, there is no significant relationship between any of the measured physiological changes and the total of the symptoms produced. It is of interest that the symptom questionnaire supposedly samples many things that should reflect the physiological changes, i. e., "Do you feel ill; are you nauseated; are you hot; are you cold; are you sweating; are your palms moist; do you feel weak?" This suggests that the subjective effects are to some degree related to some factor or factors that are independent of the somatic pharmacological activity, whereas the objective effects are more closely related to the somatic pharmacological action of this drug. In a previous report it was shown that these subjective effects are related to a number of personality variables.<sup>5</sup> The greater the personality deviation of the subject, the greater the subjective effect of the drug. This is true for the objective psychological effects but not to the same degree.

Generalization of this finding to other drugs must be questioned, for it may be argued that the failure of the subject to perceive accurately the extent of his own

physiological change is a function of the distortions in perception caused by LSD.

### Summary

Ten subjects were given 100 $\gamma$  of lysergic acid diethylamide (LSD), as well as two placebos on separate days. A number of physiological measures were recorded, as well as objective and subjective psychological effects of this drug. The results indicate that the physiological effects of LSD are significantly correlated with objective psychological effects, but not with subjective psychological effects.

Laboratory of Clinical Science, National Institute of Mental Health (14).

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TABLE 2.—Coefficient of Correlation Between Physiological and Psychological Effects of 100 $\gamma$  of LSD

	Blood Pressure	Pulse	Respiration	Temperature
Objective psychol.	0.65*	0.68*	-0.03	0.86†
Subjective psychol.	-0.12	-0.51	-0.15	0.42

\*  $P < 0.05$ .†  $P < 0.01$ .

## Clinical Notes, New Instruments and Techniques

### A Vernier Scale for Measuring Time on Electroencephalogram or Polygraph Chart

LUTHER L. MAYS, Ph.D., Washington, D. C.

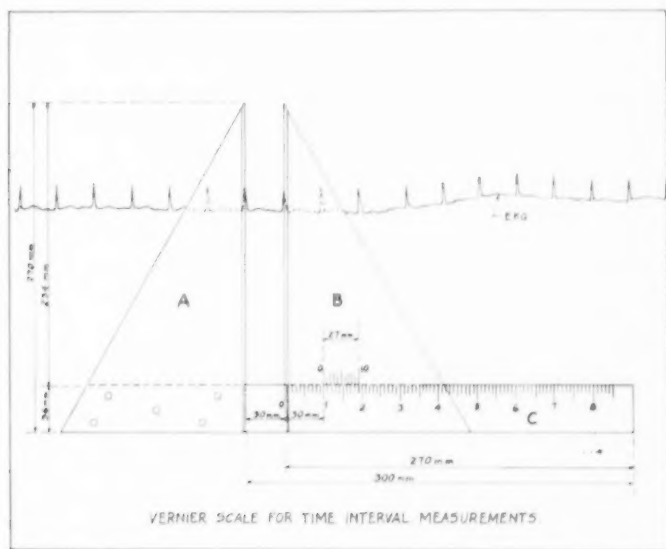
The electroencephalograph is often used as a polygraph for recording psychophysiological responses, such as the electrocardiogram, respiration, muscle potentials, and the like. After making a recording of such responses, the investigator frequently wishes to measure large numbers of time intervals. He may wish to know the duration of each successive cycle of respiration or of successive groups of four heartbeats or the time elapsing between the presentation of a stimulus and the beginning of a response. He typically makes the measurements of such intervals with a millimeter "ruler," or

scale, placed on the paper chart on which the responses have been recorded.

When making these measurements, the investigator runs into several difficulties. It is not easy for the eye quickly and accurately to pick out the point on the millimeter scale which is exactly opposite, for example, the peak of a given heartbeat recorded on the chart. Fractional parts of a millimeter must be estimated. If the millimeter scale is lined up from the peak of one heartbeat to the peak of a succeeding one, the scale is frequently at an angle rather than parallel to the edge of the chart, due to base-line sway or to variations in the amplitude of the R-wave or both. As a result, the reading

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James Wood, of the Veterans of Foreign Wars, made the drawing.



is in error, since time is correctly represented only by distances measured parallel to the edge of the chart. Finally, when the numerical value of the measurement is obtained, it is in millimeters and must be multiplied by a constant in order to convert it into seconds.

The instrument shown in the Figure (constructed by a local instrument maker according to the general design furnished by me) reduces or eliminates all these difficulties. It consists essentially of two parts, as follows: 1. A plexiglas triangle, *A*, with scale *C* (of the same material), permanently fastened thereto. *A* and *C* thus form a single unit. 2. Plexiglas triangle *B*, which is a completely separate unit, in no way attached to either *A* or *C*. *B* can, therefore, slide freely to the left or right, along the upper edge of scale *C*. Note that a short vernier (scale) is inscribed along the lower edge of *B*. This vernier together with scale *C* forms a complete vernier scale. The markings which form the two scales are so positioned on the Plexiglas that when the zero points of the two scales are directly in line with each other, the vertical (left) edge of triangle *B* is touching the vertical (right) edge of triangle *A*. A zero reading thus indicates that the distance between the two triangles is zero. If *B* is moved away from *A*, toward the right, the horizontal distance lying between the vertical edges of the two triangles is indicated at any moment by the reading taken from the two scales in the usual manner of reading a vernier. The spacings of the divisions and subdivisions of the scale are such that the reading obtained will be in units of time (seconds and hundredths of a second) rather than in units of distance (such as millimeters), assuming the record was taken at the usual paper speed of 30 mm/sec.

In order to use the instrument, the chart from which measurements are to be taken is placed upon a drawing board having a straight edge, with the lower edge of the chart resting against the straight edge. The two units of the instrument (*A-C* and *B*) are

then placed on top of the chart, with the lower edge of *A-C* against the straight edge and the lower edge of *B* resting against the upper edge of scale *C*. The instrument is now set up for operation. The Figure shows it being used to measure the time elapsing between two successive heartbeats of an EKG recording. *A-C* is moved along the straight edge until the vertical (right) edge of triangle *A* is directly over the peak of the first of the two heartbeats. *B* is then moved along the upper edge of scale *C* until the vertical (left) edge of *B* is directly over the peak of the next heartbeat. The time elapsing between the two heartbeats can then be read directly from the scale. The scale reading for the pair of heartbeats being measured in the Figure is exactly one second. In order to measure the time elapsing between a second pair of heartbeats, it is necessary only to slide *A-C* and *B* along the chart until the vertical edge of *A* is directly over the first heartbeat of the new pair and the vertical edge of *B* over the second; the new reading is then taken. Measurements of reaction time, the duration of a respiratory cycle, or other phenomena are taken in the same manner.

The instrument has a number of advantages over the ordinary "ruler" type of millimeter scale. It is much easier to align the edges of the Plexiglas triangles with points on the chart, such as the peaks of heartbeats, than it is to position a millimeter scale between the points. It is easier to take a reading from the vernier scale, once the triangles have been positioned, than to try to take a reading with the eye glued on both a millimeter scale and a point on the chart simultaneously, as is necessary when using the latter type of scale. Fractional parts of a unit do not have to be estimated, since the vernier gives readings in units so small that fractional parts are of no significance. Neither base-line sway nor variations in amplitude have any effect on the reading, since the instrument measures distance parallel to the edge of the chart only; the initial point of the interval being meas-



ured may be several inches below or above the terminal point without affecting the measurement. As a result, it is just as easy to measure the time elapsing between a given event, as indicated on channel 1 of the chart, and another event on, say, channel 8 as to measure the time between two points on the same channel. This is of particular value when measuring reaction time, since the stimulus mark and the recorded indication of the response usually appear on different channels. Finally, the readings are more accurate and are obtained in seconds and hundredths of a second rather than in millimeters, so that no conversion from space units to time units is required.

#### Details of Construction

Triangle *A* is composed of two layers of Plexiglas, each layer being  $\frac{1}{8}$  in. in thickness. The surface dimensions are as shown in the Figure. The two layers are fastened together with small machine screws (not shown). The bottom triangular layer extends only to the upper edge of the Plexiglas strip, *C*, which is also  $\frac{1}{8}$  in. in thickness. *C* extends throughout the entire width of the base of *A*. Thus, the base of the triangle forming the bottom layer of *A* fits against the upper edge of *C*, the surface of this layer being level with the surface of *C*. The top triangular layer of *A* extends downward all the way across the top of strip *C* to the lower edge of *C*. It is fastened to *C* with machine screws, the heads of which appear in the Figure. Thus, the top layer of *A* is larger than the bottom layer, since the top layer extends across the width of *C*, whereas the bottom layer does not. Since strip *C* and the bottom layer of *A* are both fastened to the top layer of *A*, these three pieces form a single unit, after construction is completed.

Triangle *B* is constructed in the same manner as triangle *A*, except that the top layer of *B* is not fastened to *C*. The top

layer extends across *C* in the same manner as the top layer of *A*, but is unattached to *C*.

The two triangles, *A* and *B*, are, of course, right-angled triangles. The angle at the apex of each is 30 degrees in the instrument shown, but could be of any desired magnitude. The vertical side of each Plexiglas triangle is beveled so that it has a sharp-line edge, which can be accurately aligned with a given point on the chart from which measurements are being taken. All parts of the instrument except the top layer of *B* are made of snow-white, nontransparent Plexiglas; this color is used in order to provide good contrast for the scale markings. The top layer of *B*, however, is made of clear, transparent material.

The vernier-scale markings on *B* are inscribed on the surface of the bottom layer of this triangle. They are read through the top, transparent layer. This top layer of *B* is made to extend across the top of *C* (as noted above) so that the scale markings on *C* will also be read through a layer of Plexiglas, thus equalizing the effects of refraction for scale *C* and the vernier on *B*.

Each of the main (numbered) divisions of scale *C* is 30 mm. in length and is, therefore, equivalent to one second on an EEG chart which has been recorded at the standard paper speed of 30 mm/sec. Each of the 10 subdivisions within a given main division is 3 mm. and hence represents 0.1 second. The vernier scale on *B* is 27 mm. in length (nine-tenths as long as one main division on scale *C*), with the result that each of its 10 subdivisions represents 0.01 second when read in conjunction with scale *C*. The two scales must be inscribed on *B* and *C*, respectively, in such positions that the zero marks of the two are in perfect alignment when the vertical edges of the two triangles are touching and are coincident with each other. In order for the scales to be accurate, they should be inscribed with a linear dividing engine by an instrument maker or a machinist.

VA Hospital, 2650 Wisconsin Ave. N.W. (7).

## Books

### BOOK REVIEWS

**Theories of Personality.** By C. S. Hall and G. Lindzey. Price \$6.50. Pp. 572. John Wiley & Sons, Inc., 440 Fourth Ave., New York 16, 1957.

Two professors of psychology have collaborated to present the main current theories of personality, as represented by Freud, Jung, Sullivan, Murray, Levin, Allport, Rogers, Murphy, and several others not identified with specific names. Most of the leaders in psychology and psychiatry develop their concepts and methodology through a lifetime of work and gradually sharpen or change their ideas. Rarely do they organize their concepts into a global scheme that could be called *their* theory. Therefore the authors were compelled to read a tremendous amount to extract material from which to cull each theory. This prodigious task is extremely valuable for the student of personality, for within one volume are the essential features of the significant theories of our time.

The book begins with an excellent chapter on the "Nature of Personality Theory" and ends with a discussion of "Personality Theory in Perspective." Here they compare the various theories and criticize them in general. All these theories have defects and yet have been stimulating to further research. No synthesis into one grand theory seems possible at this time.

The book is excellently written, and its contents are well chosen. There are extensive bibliography at the end of each chapter and an adequate index. This volume is highly recommended.

**La thérapeutique par la chlorpromazine en pratique psychiatrique.** By L. Revol. Price, 800 fr. Pp. 150. Masson & Cie, 120 boulevard Saint-Germain, Paris 6<sup>e</sup>, 1956.

This monograph by the professor of medicine and of pharmacy at Lyon, with the collaboration of numerous psychiatrists in the psychiatric hospitals of the neighborhood, is essentially an account of the experience of this group, which has been investigating the effects of the drug since its introduction, on more than 2000 patients.

The monograph is divided into three parts, of which the first contains the history of the discovery of the drug and of its application in psychiatry, its constitution and pharmacological properties, and its biological effects on man; the second part discusses its clinical applications in psychiatry, and the third part, the mode of administration, conditions under which it is to be used, its complications, and contraindications.

In general, the monograph contains nothing new or different from the many reports which have appeared in our literature, and an American psychiatrist would have little to gain from reading it. The statements of the authors, however, are eminently reasonable, and the conclusions that they draw may well be remembered by all practitioners who use the drug. They point out that, even under the present insufficient conditions in the hospitals, the number of patients who can be discharged is increased and the period of stay in the hospital shortened, and this has made some people think that many patients may be treated by the local general practitioners, without recourse to placement in the hospital. They warn, however, that, if this is to take place, the general practitioner must be better prepared to handle psychiatric cases than he is at present because the drug is not a specific curative drug which strikes at the etiological factor. It is one of those ubiquitous therapeutic agents without specificity (such as antibiotics) which help the patient to resist his disease or make him more accessible to the therapeutic action of his physician. Therefore, unless the general practitioner is better trained in psychiatry, the utilization of this drug will result in the necessity for the multiplication of mental health clinics where the patients can be given preventive treatment which will avoid the necessity of hospitalization. The increased number of patients made accessible to such therapy as psychotherapy, occupational therapy, etc., will necessitate a considerable increase in the therapeutic personnel in our mental hospitals and also the multiplication of rehabilitation centers, where the patients can be followed and treated after their discharge from the hospital, since in most cases the drug will have to be given for a considerable period of time. Such rehabilitation will necessitate an increase in the number of convalescent centers, day clinics, night clinics, supervision of placement, etc. If the environment to which the patient is discharged is not carefully controlled, a relapse occurs in spite of the continuation of the drug.

## BOOKS

There is no need to summarize the details of methods of administration of the drug, of its complications and indications, since this information is easily available to the physicians in English. One should be thankful, however, for the careful and abundant bibliography, which is rather unusual in French books and will be very helpful as a guide to the original literature in the French language.

This monograph may be heartily recommended as an eminently reasonable account of a considerable experience with the use of chlorpromazine.

### **Application of Basic Science Techniques to Psychiatric Research.** Price, \$2.00. Pp. 211.

Psychiatric Research Reports of the American Psychiatric Association, The American Psychiatric Association, 1270 Ave. of the Americas, New York 20, 1956.

This sixth psychiatric research report is probably one of the best of the very good reports previously published. The contributors are all experts in the various techniques which they present, and they write with sufficient clarity that they can be understood by persons in all disciplines. There is no attempt to summarize or to integrate the various approaches in psychiatric research. This is a task which is far too difficult at the present time. However, in Kubie's brilliant address on the use of psychoanalysis as a research tool and the discussion of this presentation by Leo Rangell, there is some indication that the concepts of various disciplines may be analogous. At the end of the symposium, Abraham Kaplan presents the philosophical point of view, which in general attempts to synthesize the various approaches. No matter if it is not possible at this time to make such a synthesis, the individual presentations are of such high caliber that they should not pass unread by all people even remotely concerned with psychiatric research. Certainly, The American Psychiatric Association, and especially the Committee on Research, should be congratulated on turning out so many excellent research reports. These are not just relishes of old papers or of time-worn concepts. They really represent what is significant in psychiatric research today.

### **Personality, Stress and Tuberculosis.** Edited by Phineas J. Sparer, M.D. Price, \$12.50. International Universities Press, Inc., 227 W. 13th St., New York 11, 1956.

Through the ages poets and authors have written about the psychological processes in tuberculous patients. Tremendous interest is evidenced in operas and dramas as well. But the psychological aspects of tuberculosis have only lately been carefully studied.

At the Veterans Administration Hospital in Memphis several symposiums were held concerning this problem, at which various authorities in the field of tuberculosis, stress, psychology, and psychiatry presented their conclusions. Dr. Sparer has collected these addresses and published them in book form, making them easily accessible to persons concerned in this field. Each contribution is excellent and is worthy of study, not only for a better understanding of tuberculosis but for information regarding stress effects in general. There is an adequate index, and each chapter has its comprehensive bibliography.

### **Straight to the Heart.** By George Lawton. Price, \$5.00. Pp. 347. International Universities Press, Inc., 227 W. 13th St., New York 11, 1957.

As new procedures and operations develop with the progress of medicine, psychological problems appear in patients who are subjected to these therapies. One of the outstanding problems now confronting psychiatrists is the understanding in therapy of persons undergoing radical and serious operations on the heart.

George Lawton, who is a psychologist, had to have a serious operation and recounts his feelings from the first day he knew what had to be done until he was fully recovered. His book is of value for lay people who are about to enter into this form of therapy and for psychiatrists who will increasingly be called upon to deal with such patients.

The book is written from the standpoint of an ordinary human being suffering from serious emotional disturbances during the whole procedure of preparation for the operation, the actual operation, and the postoperative period. In one chapter the author's psychological knowledge is expressed in a parody entitled, "Who Killed Cock Robin?" He starts out with the following questions: "Why did this have to happen . . . and to me? What did others do to me, what did I do to myself, that brings me to the end of the road?" The chapter is a fascinating rendition of a patient's hostilities and guilts and ends with the following paragraph:

"For the dead man rose, walked slowly up to his parents and said, 'Mama, and you Pop, you both heard what the Judge said. No one was killed, no one was murdered. It is no one's fault, 'now or ever,' as the good Judge said. I just died, that's all. And it all happened a

long time ago. What can't be changed always seems to have happened a long time ago. I'm sorry, you're sorry, we're all sorry.' He then kissed his mother and then his father. 'In your way you were good parents. You did the best you knew how. That's all any of us can do. Still, I must confess that I found it a terrible problem to break the news to you that I needed heart surgery. It was a much greater problem to me than I allowed myself to think at the time. I rehearsed and rehearsed the scene with you. And you know why: just because I was unable to face at the time the full force of my anger and bitterness toward you for having allowed me to get rheumatic fever.' If I had been willing to accept my own resentment toward you, the breaking-the-news-scene would have been easier to handle. But now that is all over. I have no resentments. I love you and I know you loved me and love me now. Good-by.'

"Spreading his arms so as to include every defendant, the dead man said, 'I forgive you all. I forgive even you, rheumatic fever germ. And I forgive—most of all—I forgive myself.'"

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2. Pence, L. M.: *Texas State J. Med.* 50:290 (May) 1954.
3. Berman, B. A.: *Am. J. Psychiat.* 112:541 (Jan.) 1956.



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0.25 mg. (scored) and 0.1 mg.

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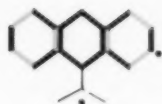
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1. Rockmore, L.; Shatin, L., and Funk, I.C.: *Psychiat. Quart.* 30:189 (April) 1956.

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